CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-451

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-451**
SERIAL NUMBER:	**2**
DATE RECEIVED BY CENTER:	**6/20/2003 and 9/22/2003**
DRUG NAME:	**Oraqix® Peridontal Gel (lidocaine 2.5% and prilocaine 2.5%)**
INDICATION:	**Localized anesthesia in periodontal pockets for ——— , scaling and/or root planing**
SPONSOR:	**Dentsply Pharmaceutical (York, PA)**
DOCUMENTS REVIEWED:	**N 000 AZ and N 000 BZ**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care & Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**R. Daniel Mellon, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
PROJECT MANAGER:	**Kimberly Compton**

Date of review submission to Division File System (DFS): December 19, 2003

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on Approvability

From a non-clinical pharmacology and toxicology perspective, NDA 21-451 is approvable.

1.2 Recommendation for nonclinical studies

The sponsor committed to conduct a Segment III reproductive toxicology study for prilocaine in a single species using currently accepted study protocols. This study was required, as the 1964 study (Document E16) did not provide sufficient data on the sensory functions and reflexes or behavior of the F_1 generation for prilocaine. This study will be completed as a Phase 4 commitment with dosing being initiated no later than July of 2004.

1.3 Recommendations on labeling

A labeling review was completed and negotiated with the sponsor. Specific details regarding the studies to be included in the Carcinogenesis, Mutagenesis, Impairment of Fertility section and the Pregnancy section are listed in the Suggested Labeling portion of the Overall Conclusions and Recommendations section of this review. The comparison of human exposure to the animal exposures in the studies assumes 100% bioavailability of lidocaine and prilocaine. The comparisons for o-toluidine also assume 100% conversion of prilocaine to o-toluidine. This assumption was made to provide the worst-case analysis following consultation with Dr. David Lee, the Biopharmaceutics reviewer. Dr. Lee indicated that the information submitted by the sponsor to support their claim that lidocaine and prilocaine have a maximal absorption of 40% were not adequate.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings

This is the second cycle review of NDA 21-451. Although the NDA was considered "approvable" from the pharmacology/toxicology perspective at the end of the first review cycle, Dr. McGovern indicated that there were outstanding genetic toxicology and reproductive toxicology issues that remained to be resolved. As stated in the approvable letter sent to the sponsor:

Before the application may be approved, however, it will be necessary for you to:

1. Submit the following studies to address the genotoxic potential of prilocaine:

a. an *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay.

b. an *in vivo* test for chromosomal damage using rodent hematopoietic cells. This study is requested as a previously submitted *in vivo* mouse micronucleus assay did not demonstrate sufficient toxicity at the highest dose tested.

2. Submit the following studies to address the reproductive toxicity potential of prilocaine:

a. a fertility study with lidocaine.

b. embryo-fetal development studies in rabbits with lidocaine and prilocaine.

c. pre- and post-natal development studies with lidocaine and prilocaine.

To fulfill these requests for the second cycle of the review process, the sponsor completed an *in vitro* chromosomal aberrations assay in human lymphocytes with prilocaine. The results indicated that under the conditions tested, prilocaine did not demonstrate any evidence of clastogenicity. The results of the study were incorporated into the label.

Drs. Habemy and McGovern indicated that the *in vivo* mouse micronucleus assay submitted for first review of the NDA was not valid since it did not test sufficiently high doses. In the post-action meeting, the sponsor acknowledged that the submitted study did not contain any data that would indicate that the high dose tested was the maximum tolerated dose. However, they noted that the study itself did contain descriptions of the dose-range finding study completed to determine doses in the submitted study. In addition, the sponsor indicated that they also have clinical observations made during the definitive study that indicates that the high dose was a maximum tolerated dose. The Division told the sponsor that their proposal to amend the *in vivo* mouse micronucleus report with pilot study data and clinical observations from the main study to support dose selection was acceptable, but that the information would be required to be reviewed to determine adequacy of the study.

The additional data in the amended report for the *in vivo* mouse micronucleus assay of prilocaine included clinical observations recorded during the definitive study and preliminary dose-range finding studies. These observations noted that two of 4 (50%) male mice had clonic convulsions about 1.5 hours after receiving a dose of 400 mg/kg, s.c., and two other males were sedated for longer than 1.5 hours. There were no seizures in the female animals at the 400 mg/kg dose; however, the amended report indicated that females treated with 400 mg/kg were sedated for approximately 2-4 hours. Convulsions indicate that 400 mg/kg, s.c. actually *exceeded* the maximum tolerated dose in males. Mortality occurred in one male administered 500 mg/kg and 2 females administered 600 mg/kg, s.c. The maximum tolerated dose in females was not clear from the additional data. The clinical description of prolonged sedation in females and males implies a

clear CNS toxicity and suggests a similar susceptibility to prilocaine toxicity. As such, the dose of 400 mg/kg appears to be a maximum dose in this species. Based upon the clinical observations in the main study and the description of the dose range finding study in the amendment to the original study report, a prilocaine dose of 400 mg/kg, s.c. is adequate. Therefore, the results of the *in vitro* chromosomal aberrations assay indicated that prilocaine is not clastogenic under the conditions of the assay. Although not requested, the sponsor also amended the original study report on lidocaine in a similar fashion which further supports the dosing employed.

To complete the characterization of the effects of lidocaine and prilocaine on reproduction, the sponsor submitted six additional study reports describing results of studies that were conducted in the 1960s and 1980s. During the post-action meeting, the Division indicated that the sponsor may submit these studies to respond to the requirements outlined in the approvable letter. However, the Division indicated that the studies would have to be reviewed for adequacy.

Segment II studies for lidocaine were completed in the rat and rabbit models. Treatment of male rats with lidocaine (30 mg/kg, s.c.; 180 mg/m^2, approximately equivalent to the maximum recommended human dose per session assuming 100% bioavailability) for 9 weeks prior to mating did not alter the fertility of male rats. Likewise, treatment of female rats with 30 mg/kg, s.c. lidocaine for 2 weeks prior to mating through day 14 of pregnancy did not produce any alterations in reproductive performance nor embryonic toxicity. In the rabbit, treatment with lidocaine at a dose of 5 mg/kg, s.c. (60 mg/m^2; 0.4-fold the maximum recommended human dose per session assuming 100% bioavailability) from day 6 through 18 of pregnancy did not produce any teratogenic effects. A dose of 15 mg/kg, s.c. (180 mg/m^2; 1.4-fold the maximum recommended human dose per session assuming 100% bioavailability) did not produce evidence of teratogenicity. The non-significant findings of slightly decreased mean fetal body weight and increased minor skeletal abnormalities are suggestive of potential fetotoxicity at this dose.

The sponsor provided data to assess the potential toxic effects of prilocaine on embryo-fetal development in the rabbit model. The study was originally completed to test the effects of Citanest-Octapressin (Prilocaine-Vasopressin), a combination drug product (0.033, 0.33, 1.7 ml/kg) on embryonic development. The dose of prilocaine in this study corresponded to 0, 1, 10 and 50 mg/kg, s.c. Female rabbits were treated from day 6 through 18 of pregnancy. There were no effects of drug treatment on the number of implantation sites, litter size, litter and mean pup weight between treatment groups. However, there were several abnormalities noted, including one pup with spina bifida of a lumbar vertebra, a major abnormality. The fact that the only observation was in the low-dose group and no other major abnormalities occurred at higher doses supports the conclusion that the finding does not appear to be related to the test article. The sponsor interpreted the finding as a spontaneous event. Retrospective examination of the

incidence of spontaneous major malformations detected at the ——— ——— (where the study was conducted) in the New Zealand White Rabbit was 55 cases out of 8036 fetuses. Further, the incidence of spina bifida at this facility was 1 out of 8036 fetuses examined (0.01%). A search of the Historical Control Database of Pre-Clinical Developmental Teratology and Reproductive Toxicity Parameters ——— detected 1 fetus out of 13820 evaluated to present with the abnormality "External Abnormality: Trunk – Spina Bifida" in rabbits of any strain or stock[1]. The low incidence of this malformation in the historical databases raised significant concern. Since this effect occurred in a low-dose animal and not other neural-tube defects were noted in other animals, the effect does not appear to be treatment-related. As such, although the study was of a combination drug, the exposure to procaine in the study was sufficient to conclude that there was no evidence for prilocaine induced teratogenicity, under the conditions tested.

Studies to address the effects of lidocaine on the peri- and postnatal development (Segment III) in rats were conducted via both the subcutaneous and intramuscular route of administration. Rats were treated with lidocaine (0, 1, 5, or 10 mg/kg, s.c). from day 15 of pregnancy to day 10 postparturition (weening). Observations of the litters from the high dose group (10 mg/kg, s.c.; 60 mg/m^2; 0.5-fold the maximum recommended human dose per session assuming 100% bioavailability) detected a slight decrease in litter size and number of litter pups and increased pup loss. In contrast, there were no differences in mean pup weights or time to occurrence of physical developmental milestones or the types/frequencies of gross malformations between groups. However, the high dose also produced evidence of maternal toxicity including decreased weight gain, decreased food consumption and prolongation of the gestation period. There were no adverse effects in either the dams or the pups at the dose of 5 mg/kg, s.c. (30 mg/m^2). A second study was conducted via the intramuscular route of administration. Lidocaine (6 mg/kg, i.m.; 36 mg/m^2, 0.2-fold the maximum recommended human dose per session assuming 100% bioavailability) was bilaterally injected intramuscularly on pregnancy day 10 and 11. Development of the offspring was monitored via tests of spontaneous activity, nociception, learning ability and physical development. Under the conditions of the study, the pups from the lidocaine group were comparable to those from the vehicle group.

Finally, the sponsor provided a report from 1964 where lidocaine or prilocaine (10 or 30 mg/kg, s.c.) was administered daily for 8 months to both male and females. A total of three mating periods were obtained and pups were examined for developmental abnormalities at birth and at weaning. Treatment of the F_0 generation with either dose of lidocaine or prilocaine did not alter the number of litters produced, the mean number of pups born per litter, the mean weight of pups at birth and the weaning or the distribution of sex among pups. However, treatment with either dose of lidocaine or prilocaine (10 or 30 mg/kg, s.c.)

[1] Search was conducted on December 12, 2003 (http://www.hcd.org/).

produced a significant decrease in the average number of pups per litter surviving until weaning. The study concludes that neither lidocaine nor prilocaine altered the reproductive potential of the rat. Technically, this study does not fully address the post-natal development effects of prilocaine or lidocaine, since f the F_1 generation was not tested for reproductive capacity, behavioral testing or reflex testing.

2.2 Pharmacologic activity

Local anesthetics block conduction in excitable tissue by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Local anesthetics can also bind to other membrane proteins such as K^+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K^+ channels since the interaction of local anesthetics with K^+ channels requires higher drug concentrations. Lidocaine and prilocaine have similar pharmacological profiles and are about equipotent. Lidocaine is considered to be the faster acting of the two components, although is shorter-acting in comparison to the long-acting drug bupivacaine. Prilocaine causes little vasodilation and can be used without a vasoconstrictor and its increased volume of distribution reduces its CNS toxicity.

2.3 Nonclinical safety issues relevant to clinical use

Based upon the information provided and our understanding of the drug substances at this time, there does not appear to be any safety issues with the clinical use of this drug product.

[Please limit to 1-3 pages]

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number:	21-451
Review number:	2
Sequence number/date/type of submission:	N 000 B2 / 6-20-2003 / Amendment N 000 B2 / 9-22-2003 / Amendment
Information to sponsor:	Yes ( ) No ( )
Sponsor and/or agent:	DENTSPLY Pharmaceuticals York, PA
Manufacturer for drug substance:	AstraZeneca, AB Bjorkborn, Sweden

Reviewer name:	R. Daniel Mellon, Ph.D.
Division name:	Anesthetic, Critical Care & Addiction Drug Products
HFD #:	170
Review completion date:	December 19, 2003

Drug:

Trade name: Oraqix® Periodontal Gel

Generic names: lidocaine; prilocaine

Code name: Lidocaine, Xylocaine
Prilocaine, Citanest, L67

Chemical names:

Lidocaine: 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide

Prilocaine: N-(2-methyl-phenyl)-2-(propylamino)-propanamide

CAS registry numbers:

Lidocaine: 137-58-6

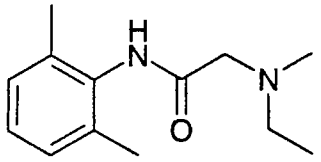
Prilocaine: 721-50-6

Molecular formula/molecular weights:

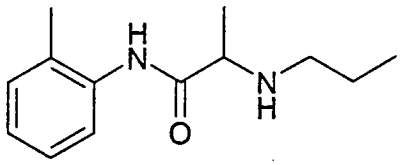
Lidocaine: $C_{14}H_{22}N_2O$ / 234.3

Prilocaine: $C_{13}H_{20}N_2O$ / 220.3

Structures:



Lidocaine



Prilocaine

Relevant INDs/NDAs/DMFs: IND 52,677 (Oraqix®); NDA 19-941 (EMLA Cream)

Drug class: Both drugs belong to the amide class of local anesthetics.

Indication: Oraqix® is indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing.

Clinical formulation:

Ingredient	Quantity (mg)	Function
Lidocaine	25	
Prilocaine	25	
Poloxamer 188 purified	[redacted]	[redacted]
Poloxamer 407 purified		
Hydrochloric acid, Ph. Eur., NF	[redacted]	
Water purified, Ph. Eur., USP		

Route of administration: Oral absorption across the mucous membrane (dental gel for oral mucosa).

Proposed use: On average, one cartridge (1.7 g) or less will be sufficient for one quadrant of the dentition. The maximum recommended dose of Oraqix® at one treatment session is 5 cartridges (8.5 g gel containing 212.5 mg lidocaine base and 212.5 mg prilocaine base). The periodontal pockets should be filled with Oraqix® until the gel becomes visible at the gingival margin. The duration of anesthesia is about 20 minutes. If anesthesia starts to wear off, Oraqix® is reapplied as needed.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise. In addition, sections of the introductory text were taken directly from the Original NDA Pharmacology and Toxicology Review by Drs. Kathleen Haberny and Timothy McGovern.

Studies reviewed within this submission:

Study Title	Document #	Volume	Review / Date
Genotoxicity:			
Prilocaine hydrochloride: Chromosomal aberrations in cultured human peripheral blood lymphocytes	7104-112	3	N21-451, 12/03
Mouse micronucleus test of prilocaine.	T1968-02	3	N21-451, 12/03
Mouse micronucleus test of lidocaine hydrochloride monohydrate (LEA1523).	T2362-02	3	N21-451, 12/03
Reproductive Toxicity			
Effects upon fertility and general reproductive performance in rats of Xylocaine given subcutaneously.	T1593	3 of 3	N21-451, 12/03
The effects upon pregnancy in rabbits of Xylocaine given subcutaneously.	T1442		N21-451, 12/03
Effects of Citanest-Octapressin solution on pregnancy of the New Zealand White rabbit.	ET177	3 of 3	N21-451, 12/03
The effect of adrenaline on the toxicities and absorptions of L67 (Citanest) and some other local anaesthetics studied in mice and rabbits. Acta Pharmacol Toxicol 1964, 21:161-171.	N/A	3 of 3	N21-451, 12/03
Effects upon peri- and postnatal development in rats of Xylocaine given subcutaneously.	T1756	3 of 3	N21-451, 12/03
Effects upon pregnancy and offspring development in rats	T1781	3 of 3	N21-451, 12/03

of Lidocaine given intramuscularly with special reference to behavioral effects.			
Reproduction study of Citanest and Xylocaine.	E16	3 of 3	N21-451, 12/03

Studies not reviewed within this submission (previously reviewed for Original NDA or NDA 19-941):

Study Title	Document #	Volume	Review / Date
Pharmacology:			
Percutaneous local anesthesia in the guinea pig by emulsions of an eutectic mixture of Citanest and Xylocaine	802-10 A 135-02	5	N19-941, 1/89
Topical local anesthetic effect of an eutectic mixture of Citanest and Xylocaine on abraded skin in the guinea pig	802-10 A 137-02	5	N19-941, 1/89
Pharmacokinetics and Toxicokinetics:			
Evaluation of plasma concentrations of lidocaine and prilocaine in the study: General toxicity of EMLA given rectally to dogs for one month	802-10 AF 42-1	6	N19-941, 11/99
Toxicology:			
Acute toxicity of Xylocaine and Citanest (1:1) in male mice after IV injection	T1349	6	N19-941, 1/89
Acute toxicity of Xylocaine and Citanest (1:1) in male rats after IV injection	T1330	6	N19-941, 1/89
Acute toxicity of lidocaine, prilocaine and EMLA in male rats after SC injection	T1372	6	N19-941, 1/89
Acute toxicity of EMLA cream in rabbits after single dermal administration	T1373	6	N19-941, 1/89
General toxicity of EMLA given rectally to dogs for one month	T1608	6	N19-941, 11/99
Lidocaine hydrochloride monohydrate (ARP111001UZ): Single oral (gavage) MTD study in rats	SR00609-01	8	N21-451, 11/02
Prilocaine hydrochloride (AR-P111002AA): Single oral (gavage) MTD study in rats	SR01048-01	8	N21-451, 11/02
Genotoxicity:			
Mutagenicity evaluation of LEA152 in the Ames Salmonella/Mammalian microsome mutagenicity test	T2355	7	N19-941, 6/92
Analysis of structural chromosome aberrations in human lymphocytes treated with lidocaine HCl monohydrate (LEA152) in vitro	T2376	7	N19-941, 6/92
Mouse micronucleus test of lidocaine HCl monohydrate	T2362	7	N19-941, 6/92
Mutagenicity evaluation of 2,6-xylidine in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test	T2183	6	?
Lidocaine hydrochloride monohydrate (ARP111001UZ): Single oral (gavage) MTD study in rats	SR00609-01	8	N 21-451, 11/02
Prilocaine hydrochloride (AR-P111002AA): Single oral (gavage) MTD study in rats	SR01048-01	8	N 21-451, 11/02
Reproductive Toxicology:			

Effects on pregnancy in rats of a lidocaine:prilocaine (1:1) mixture given SC – a DRF study	T2412	7	N19-941, 6/92
Effects on pregnancy in rats of a lidocaine:prilocaine (1:1) mixture given SC	T2413	7	N19-941, 6/92
Special Toxicology:			
Vaginal irritation, in dogs, after topical administration of Xylocaine/Citanest (EMLA) on 20 consecutive days	T1163	7	N19-941, 1/89 N19-941, 11/99
Irritation of intact skin, in rabbits, after 24 hours occlusive epicutaneous administration of Xylocaine/Citanest emulsion	T1017	7	N19-941, 1/89
Skin irritation, in the rabbit, after epicutaneous application of Xylocaine/Citanest (EBLA) for 1 hr a day on 20 consecutive days	T1128	7	N19-941, 1/89
Eye irritation in rabbits after single administration of Xylocaine/Citanest emulsion	T1018	7	N19-941, 1/89

3.2 PHARMACOLOGY

3.2.1 Brief summary

No new pharmacology studies were performed by the sponsor for this application. A review of the pharmacology of local anesthetics in general, and lidocaine and prilocaine specifically, is provided in Goodman and Gilman's The Pharmacological Basis of Therapeutics. When applied locally to nerve tissue in appropriate concentrations, local anesthetics reversibly block the action potentials responsible for nerve conduction. A local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The action is reversible at clinically relevant concentrations; complete recovery in nerve function occurs with no evidence of damage to nerve cell fibers or cells.

Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Local anesthetics can also bind to other membrane proteins such as K^+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K^+ channels since the interaction of local anesthetics with K^+ channels requires higher drug concentrations. Lidocaine and prilocaine have similar pharmacological profiles and are about equipotent. Lidocaine is considered to be the faster acting of the two components, although is shorter-acting compared to bupivacaine. Prilocaine causes little vasodilation and can be used without a vasoconstrictor and its increased volume of distribution reduces its CNS toxicity.

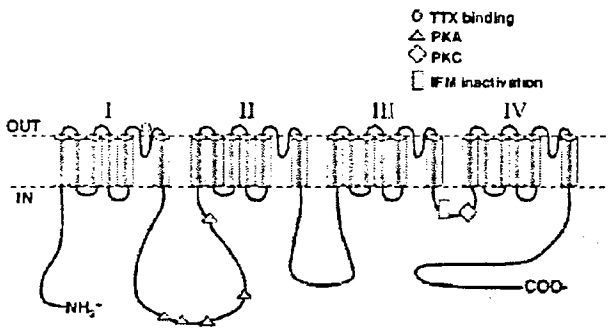
The nonclinical pharmacology studies were not conducted with the proposed clinical formulation. Pharmacology studies in guinea pigs performed under NDA 19-941 showed that eutectic mixtures of lidocaine and prilocaine over the range of 0.55 to 10% (total anesthetic base) produced a concentration-related analgesia upon a 60-minute contact

with both unabraded and abraded skin. Almost no block was observed with a 0.55% emulsion, whereas an 80% block of normal responses to pin pricking was observed with 2.5 to 10% emulsions. Analgesia lasted for approximately 60 minutes or greater. The analgesia of the combination was more profound and lasted longer than that produced by an equivalent amount of either lidocaine or prilocaine given alone. The formulations were more effective on abraded skin than on intact skin.

3.2.2 Primary pharmacodynamics

Lidocaine and prilocaine are amide-linked local anesthetics that block the conduction of nerve impulses in excitable membranes.

Mechanism of action: Local anesthetics block the generation and conduction of nerve impulses in excitable tissues by decreasing or preventing the large transient increase in the permeability of the membrane to sodium ions. Local anesthetics bind directly to sodium channels form the inside of the membrane. The degree of block produced by local anesthetics is dependent upon how the rate of nerve stimulation and on its resting membrane potential. Local anesthetics are only able to bind to sodium channels in their charged form and when the sodium channels are open. In this situation, the local anesthetic is able to bind more tightly to and stabilize the sodium channel. Differences in pKa, lipid solubility, and molecular size influence the binding of local anesthetics to sodium channels. The basic structure of a sodium channel subunit is depicted below:



Subtype	Rat Orthologs	TTX Sensitivity (nM)	Activation Threshold	Inactivation Rate	Tissue Localization
Nav1.1	Brain I	-	Low	Fast	CNS, also in DRG and motor neurons
Nav1.2	Brain IIA	18	Low	Fast	CNS
Nav1.3	Brain III	15	Low	Fast	Embryonic nervous system; adult CNS;
Nav1.4	SkM1	5	Low	Fast	Skeletal muscle
Nav1.5	H1	1,800	Low	Medium	Heart, embryonic DRG
Nav1.6	SCP5, PN4	1	Low	Fast	DRG, motor neurons, also in CNS
Nav1.7	PN1	2	Low	Fast	Mostly DRG, also in CNS
Nav1.8	PN3, SNS	>100,000	High	Slow	DRG (80% small diameter; 20% large
Nav1.9	PN5, NaN	39,000	Low	Medium	DRG (small diameter); also in CNS

Figure 1 Schematic secondary structure of the family of VGSCs. their classification. tissue distribution. and functional characteristics.

In general, small nerve fibers are more sensitive to local anesthetics than large nerve fibers. However, myelinated fibers are blocked before non-myelinated fibers of the same diameter. Autonomic fibers, small unmyclinated C fibers (mediating pain) and small myelinated Aδ fibers (mediating pain and temperature sensation) are blocked before larger myelinated Aγ, Aβ, or Aα fibers (mediating touch, pressure, muscle and postural inputs). Small, sensory fibers are preferentially blocked since nerve conduction is

more easily blocked over shorter distances and these fibers have longer action potentials allowing more of the local anesthetic to bind. Clinically, the loss of nerve function proceeds as loss of pain, temperature, touch, proprioception, and then skeletal muscle tone.

Drug activity related to proposed indication: Blockade of neuronal conduction prevents the action potential of sensory neurons and therefore blocks the transmission of pain signals to the CNS. Lidocaine and prilocaine blockade demonstrates both frequency and voltage-dependency. Both drugs block both open and inactivated Na^+ channels. The frequency dependence of this blockade makes smaller unmyelinated nerve fibers more sensitive to blockade than larger heavily myelinated fibers. Therefore, Type C fibers (dorsal root and sympathetic nerves) and Type B (preganglionic autonomic nerves) are blocked at lower concentrations than heavily myelinated Type A (alpha, beta, gamma and delta) fibers. Of the type A fibers, pain and temperature sensitive neurons (delta) are more susceptible to local anesthetics than muscle spindles (gamma), touch and pressure sensitive neurons (beta) which are, in turn, more sensitive than proprioception and motor neurons (alpha). This sensitivity also correlates with the diameter of the nerve fiber, with smaller fibers being more sensitive to the local anesthetic action.

3.2.3 Secondary pharmacodynamics

In addition to blockade of sensory nerves, local anesthetics also interfere with the functioning of all organs which require the conduction of electrical impulses for their activity. These organs include the CNS, autonomic ganglia, neuromuscular junction and all forms of muscle, including cardiac. The anti-arrhythmic effects of lidocaine are primarily due to action on the myocardium. Lidocaine leads to decreased electrical excitability, conduction rate and force of contraction.

3.2.4 Safety pharmacology

Safety pharmacology studies for either lidocaine or prilocaine were not conducted for this NDA, and are not required for drugs that have a long history of clinical use. Following overdose, local anesthetic toxicity is generally referable to the cardiovascular, neurologic and hematologic systems. Initial effects include mild hypertension and tachycardia, lightheadedness, mild agitation, and confusion. In severe cases this may progress to seizures, coma, respiratory depression, bradycardia, ventricular dysrhythmias and asystole. Prilocaine (commonly) and lidocaine (rarely) may also cause methemoglobinemia. Toxicity may result from an excessive dose, mistaken drug identity, enhanced drug absorption, inadvertent intravascular injection, altered protein binding, slowed redistribution and/or elimination.

Neurological effects: Sufficiently high blood levels (5 μg/ml) of local anesthetics can have toxic effects on the central nervous system. CNS effects can include excitation and/or depression, light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitis, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression

and arrest. In the peripheral nervous system, there is evidence that an excessively high concentration of local anesthetics can be toxic to nerve tissue.

Cardiovascular effects: Toxic CV effects may also occur with sufficiently high blood levels of lidocaine. These may include bradycardia, hypotension, cardiac collapse and arrest. Lidocaine is used therapeutically to suppress cardiac arrhythmia with effective blood concentrations ranging from 1.2 to 5 μg/ml. These effects are mediated both via direct effects on the cardiac and smooth muscle and via effects on the autonomic nerves.

Pulmonary effects: There are no known direct pulmonary effects associated with application of either lidocaine or prilocaine to the oral mucosa. With systemic dosing, apnea and respiratory depression may occur in patients with coma or seizures. Increased respirations are associated with milder forms of CNS stimulation. ARDS has been reported in patients with aspiration or during hypersensitivity reactions.

Renal effects: There are no known renal effects following topical application of lidocaine or prilocaine to the oral mucosa.

Gastrointestinal effects: Local anesthetics can depress contraction of the smooth muscle in intact bowel and strips of isolated intestine.

Abuse liability: There is no indication that lidocaine demonstrates any abuse liability. The sponsor has not conducted specific studies to examine abuse liability.

Other: Hypersensitivity: Local anesthetics can rarely cause a hypersensitivity reaction manifested as allergic dermatitis or an asthma attack. This is almost exclusively linked to anesthetics containing an ester linkage. As lidocaine and prilocaine contain an amide linkage, hypersensitivity and allergic reactions are rare, although have been reported. These reactions may be characterized by cutaneous lesions, urticaria, bronchospasm, edema, shock or anaphylaxis depending on the route of exposure.

Safety Pharmacology Summary: Formal safety pharmacology studies were not performed for this application and were not required due to the extensive human experience with both lidocaine and prilocaine. As with other local anesthetics, secondary pharmacodynamic effects of lidocaine and prilocaine include stimulation of the CNS as illustrated by restlessness and tremor leading to clonic convulsions. Central stimulation is followed by depression and death is usually caused by respiratory failure. Cardiovascular effects may include decreased electrical excitability, conduction rate, force of contraction, arteriolar dilatation, and cardiac arrhythmias when plasma levels exceed ~ 10 μmol/L (5 mg/L) for either compound. Cardiovascular effects are thought to be due to a pharmacological effect on sodium channel blockade. These findings were confirmed in acute toxicology studies performed under NDA 19-941 in which reduced motor activity, unconsciousness, respiratory distress, twitching and/or cyanosis were observed in mice and rats for up to one hour following IV administration of a 1:1 mixture. Similar findings were noted in rats following subcutaneous administration.

Lidocaine has a biphasic effect on blood flow. Lower concentrations produce vasoconstriction, while higher concentrations produce vasodilatation.

Safety Pharmacology Conclusions: The primary effects of lidocaine and prilocaine related to safety pharmacology include CNS and cardiovascular effects at plasma levels exceeding ~ 10 μmol/L (5 mg/L) for either compound. Plasma levels following administration of Oraqix® Periodontal Gel are expected to be well below the plasma levels at which these adverse findings are observed.

3.2.5 Pharmacodynamic drug interactions

Adverse Drug Interactions in Dentistry: Local Anesthetics

Drugs	Interaction	Clinical Implications
Lidocaine/prilocaine with other local anesthetics (i.e., bupivacaine)	Effects are additive	Major Significance: Local anesthetic toxicity is additive when these drugs are given in combination; although combination therapy with local anesthetics is acceptable; total dose should not exceed combined maximum recommended doses.
Procaine with sulfamethoxazole	Ester Local Anesthetics with sulfonamide antibiotics	Procaine is used infrequently; the procaine metabolite p-amino benzoic acid may transiently reduce sulfonamide antibiotic efficacy.
lidocaine with cimetadine or propranolol	Amide Local Anesthetics with Inhibitors of Metabolism	Inhibition of local anesthetic metabolism will have little effect on peak plasma levels of anesthetic when given as a single injection. Plasma clearance of lidocaine may be reduced in the presence of enzyme inducers.
Local anesthetics and opioids (i.e., mepivacaine with meperidine)	Local Anesthetics with Opioid Sedation	Sedation with opioids may increase the risk of local anesthetic toxicity, particularly with children; local anesthetic dose should be reduced.
prilocaine with dapsone	Local Anesthetic-induced methemoglobinemia	Methemoglobinemia usually results from prilocaine dosing in excess of MRD; increased risk may be possible when similar oxidizing drugs are administered.

Table Source: from Paul A. Moore. Adverse drug interactions in dental practice interactions associated with local anesthetics, sedatives and anxiolytics, JADA, vol. 130,541-554, April 1999.

Pharmacodynamic interactions can occur with either lidocaine or prilocaine in the drug product. These are outlined in the label for Oraqix®. Briefly, lidocaine may interaction with other antiarrythmic drugs which also block sodium channels and increase the toxic

effects of this class of drugs ultimately leading to seizures, heart failure or cardiac arrest. As listed in the EMLA® (lidocaine; prilocaine) label, the combination of lidocaine:prilocaine should be used with caution in patients receiving class I antiarrhythmics (e.g., disopyramide, encainide, flecainide, mexiletine, moricizine, phenytoin, procainamide, propafenone, quinidine, or tocainide) since the toxic effects are additive and potentially synergistic. Similarly, interaction with other local anesthetics would reduce the amount of lidocaine bound to α-1-acid glycoprotein and thereby increase plasma levels of lidocaine.

Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition (e.g., aniline dyes, acetaminophen, chloroquine, dapsone, fosphenytoin, naphthalene, nitrates and nitrites, nitric oxide, nitrofurantoin, nitroprusside, pamaquine, phenobarbital, phenytoin, primaquine, quinine, or sulfonamides). According to the product label, patients treated with EMLA® (lidocaine; prilocaine) who are receiving any of these agents concurrently are at greater risk for developing methemoglobinemia.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

Lidocaine and prilocaine bases are absorbed rapidly through mucous membranes, intact and damaged skin, and from the intestines and respiratory tract. The hydrochlorides are absorbed rapidly after parenteral administration, but absorption through intact skin or mucous membranes is poor. Lidocaine and prilocaine are widely distributed into highly perfused tissue, followed by redistribution into skeletal muscle and adipose tissue. Distribution is similar for both compounds although the volume of distribution is greater for prilocaine. Lidocaine affinity for melanin has been demonstrated using labeled compound resulting in a longer elimination half-life in pigmented skin. Lidocaine readily crosses the placenta and blood brain barrier with plasma levels declining in parallel that of the mother animal. Lidocaine protein binding is approximately 66% in humans and 78% in dogs. Protein binding of prilocaine in humans has been reported to be 30%, although the package label indicates 55%.

Lidocaine is almost completely metabolized before excretion with the liver as the primary site for metabolism. As such, any alteration in liver function or hepatic blood flow can have a significant effect on the pharmacokinetics and dosage requirements. Metabolism of lidocaine is qualitatively similar across species with quantitative variations. The three main types of metabolic reactions include aromatic hydroxylation, N-dealkylation and amide hydrolysis, followed by conjugation reactions. Major enzymes involved in lidocaine metabolism in human liver microsomes were CYP3A4 and CYP1A2. In a human liver slice system, MEGX and 2,6-xylidine were identified as major metabolites. In the urine of man and dogs, the major metabolite (4-hydroxy 2,6-xylidine) accounted for 70% and 35% of the dose, respectively. In rats, the urinary metabolites accounted for

70% of the administered dose and included 3-hydroxy lidocaine and its dealkylated product, 3-hydroxy-MEGX.

Prilocaine is rapidly and extensively metabolized in the liver as well to o-toluidine and its hydroxylated derivatives, as well as to N-propylalanine, in both animals and man. Most of the metabolites are excreted as conjugated as either sulphates, glucuronides, or are acetylated; enzymes involved are not known. Plasma concentrations of lidocaine generally rapidly decline after an IV dose, with an initial half-life of 30 minutes. The elimination half-life is generally 1-2 hours. There is a large variability in clearance among species with humans demonstrating a clearance of 13 ml/min kg up to 130 ml/min kg in rats. Excretion of lidocaine in breast milk has been demonstrated in humans after use in dental surgery with milk:plasma ratios for lidocaine and MEGX of 1:1 and 1:8; excretion in breast milk has not been studied in animals. Prilocaine undergoes significant elimination by extrahepatic organs, differing from other local anesthetics. The elimination half-life is generally 1.3 hours in dogs and 2.2 hours in rabbits, similar to the 1.6 hour half-life reported in humans.

Lidocaine and prilocaine bases are absorbed rapidly through mucous membranes, intact and damaged skin, and from the intestines and respiratory tract. The hydrochlorides are absorbed rapidly after parenteral administration, but absorption through intact skin or mucous membranes is poor. Both lidocaine and prilocaine are absorbed and extensively distributed and metabolized. The major metabolites include MEGX and 2,6-xylidine (lidocaine) and o-toluidine (prilocaine). Elimination half-lives across species for both compounds are in the range of 1-2 hours.

3.3.3 Absorption

The bioavailability of lidocaine following oral administration is 35%. Local anesthetics, in general, are rapidly absorbed into the circulation following topical administration.

3.3.4 Distribution

Amide local anesthetics are widely distributed after intravenous administration. Intravenous lidocaine demonstrates a rapid distribution phase (into highly perfused tissues) following by slower distribution phases into muscle as well as fat tissues. Lidocaine can cross the blood brain barrier as well as the placenta and can be detected in breast milk. Systemic lidocaine has fairly high protein binding (33-80%) in humans, primarily to α-1-acid glycoprotein. The volume of distribution has been reported to be 1.7 L/kg (Thompson et al., 1973; Rowland et al., 1971) with a distributional half-life of 15-30 minutes (Rowland et al., 1971).

Prilocaine has a fast onset of action similar to lidocaine. The total protein binding is 55%.

3.3.5 Metabolism

About 90% of the administered lidocaine is metabolized in the liver (Elvin et al. 1981; Zito and Reid, 1981). Lidocaine is not metabolized by plasma esterases. Both monoethylglycine xylidide (MGEX) and glycine xylidide (GX) exhibit some local anesthetic activity. In human beings, approximately 75% of the xylidide is excreted in the urine as 4-hydroxy-2,6-dimethylaniline. The 4-hydroxyxylidine is the predominant metabolite excreted in the urine after lidocaine administration. The conversion of lidocaine to MGEX in vitro appears to be mediated by CYP3A4 in humans and CYP2C11 and CYP2B1 in rats. There is considerable interspecies variability in the metabolism of lidocaine. N-hydroxyxylidine has been shown to form hemoglobin adducts. Xylidine-hemoglobin adducts have been detected in the blood of tobacco smokers and non-smokers.

Prilocaine is metabolized extensively in the liver. Metabolites include o-toluidine and N-n-propylalanine. The metabolite o-toluidine has been shown to form hemoglobin adducts. Therefore, the metabolites of both lidocaine and prilocaine can form hemoglobin adducts resulting in hemoglobinemia. The oxidation of normal hemoglobin by o-toluidine is dose related and methemoglobin levels in the serum can be detected following doses of prilocaine of 8 mg/kg or more.

3.3.6 Excretion

Lidocaine and its metabolites are excreted in the urine. The elimination half-life of the parent compound is between 1.5 and 2 hours (Thomson et al. 1971; Rowland et al., 1971). MEGX has a half-life of 1-6 hours and GX has a half-life of about 1 hour. The metabolite 2,6-xylidine has been detected in the breast milk of human females. Urinary excretion of local anesthetics is pH-dependent. Acidification of the urine results in increased concentrations of local anesthetics and some metabolites in urine. Alkalinization of the urine decreased levels of local anesthetics. Very little local anesthetic is eliminated in the feces of humans.

Like Lidocaine, prilocaine and its metabolites are excreted primarily in the urine. The elimination half-life ranges from 10 to 150 minutes following topical application. The half-life of prilocaine is increased in hepatic or renal dysfunction. Total body clearance is 64 ml/min/kg. For both drugs, there is some evidence for extrahepatic metabolism. In vitro studies suggest that the kidney and lung are two sites which have the capacity to metabolize lidocaine.

3.3.7 Pharmacokinetic drug interactions

Local anesthetics such as lidocaine and prilocaine are largely metabolized in the liver and therefore any alteration in liver function or blood flow through the liver will alter the plasma levels of prilocaine.

The speed of onset of a local anesthetic may be increased by the addition of a vasoconstrictor. This prevents the drug from diffusing into the general circulation from the injection site. Epinephrine is commonly combined with a local anesthetic in a ratio of 1:100,000 or 1:200,000. The total amount of epinephrine injected should not be greater than 500 mg. Local anesthetics are generally administered in an acidic solution and alkalination of the solution with sodium carbonate is thought to increase the speed of onset. Alkalinization of the solution increases the proportion of the lipid soluble nonionised free base allowing the active molecule to pass through the cell membrane. The buffering of the solution with sodium bicarbonate reduces the acidity and thereby also reduces the pain associated with their injection.

3.3.10 Tables and figures to include comparative TK summary

There were no toxicokinetic studies associated with submitted genetic and reproductive toxicology studies in this cycle.

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology: Acute toxicity studies in rats confirmed that lidocaine and prilocaine effects are primarily CNS-related and extremely high doses can induce lethality. In previously conducted studies, administration of a lidocaine/prilocaine dental gel resulted in no local toxicity, while immobility or pronounced lethargy, labored respiration, dyspnea, cyanosis and convulsions were observed with intravenous or subcutaneous administration. No local toxicity was observed following rectal or dermal application. Nonclinical information provided to support the proposed use of poloxamers 188 and 407 was described in the first NDA review and was considered to be adequate.

The systemic effects of lidocaine are summarized by the table below (reproduced from Benzon et al., 1999. Essentials of Pain Medicine and Regional Anesthesia, page 345):

Systemic Effects of Lidocaine	
Plasma Concentration (μg/ml)	**Effect**
1-5	Analgesia
5-10	Lightheadedness Tinnitis Numbness of tongue
10-15	Seizures Unconsciousness
15-25	Coma Respiratory arrest
>25	Cardiovascular Depression

Genetic toxicology: Genetic toxicology studies for **lidocaine** were performed and reviewed under NDA 19-941. Studies for prilocaine were submitted to the original NDA and the second cycle submission and are reviewed in this document. The results of these studies showed that lidocaine tested negative in an *in vitro* bacterial reverse mutation assay (Ames test), an *in vitro* assay for chromosome aberrations in human lymphocytes, and an *in vivo* mouse micronucleus assay. The lidocaine metabolite, **2,6-xylidine**, was considered weakly mutagenic (mixed results in different laboratories), and was mutagenic at the thymidine kinase locus. The compound also induced chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells at toxic concentrations. It was negative in an unscheduled DNA synthesis assay with rat hepatocytes, a chromosome aberration assay in polychromatic erythrocytes, and a differential survival assay of DNA repair proficient versus deficient *E. coli* bacteria in mouse liver, lung, kidney, testis and blood extracts.

A full battery of genetic toxicology studies has been completed for **prilocaine**. The results indicated that prilocaine tested negative in the *in vitro* bacterial reverse mutation assay (Ames test) in *S.typhimurium* strains, the *in vitro* chromosomal aberrations assay in human lymphocytes and the *in vivo* mouse micronucleus assay. The metabolite of prilocaine, **o-toluidine**, tested positively in *E. coli* DNA repair and phage-induction assays (IARC monograph, Volume 27, page 167, 1982). Urine concentrates from rats treated orally with ortho-toluidine were mutagenic in an Ames assay with metabolic activation. Several other tests were negative including an Ames assay (unless tested in the presence of both norharman and metabolic activation), and an *in vitro* chromosome aberration assay with V79 Chinese hamster cells with metabolic activation.

Carcinogenicity: Carcinogenicity testing for lidocaine and prilocaine has not been performed and are not considered necessary due to the limited duration of exposure for this drug product. However, the major metabolites (2,6-xylidine from lidocaine and o-toluidine from prilocaine) were carcinogenic in long-term studies performed in mice and/or rats. In 1993, the Anesthetic and Life Support Drugs Advisory Committee reviewed the tumor data in animals and concluded that the tumors demonstrated in the rodent models were not significant to humans. They further voted to recommend that the tumor date on 2,6-xlyidine be omitted from the package insert. CDER's Executive CAC concluded that the tumor findings are not relevant to humans and should not be included in the product labeling. In regards to o-toluidine, the sponsor was asked to provide the final o-toluidine content in the final drug product for clinical use. Also, the amount present should be limited to the lowest feasible concentration or no greater than the permitted exposure level (PEL) or Threshold Limit Value (TLV) for Chemical Substances and Physical Agents Biological Exposure Indices. The maximum annual exposure to o-toluidine is ~ 25-fold below the allowable annual intake using a TLV determined by ACGIH. The overall carcinogenic risk from o-toluidine to humans via the use of Oraqix® Periodontal Gel with the drug product specification of 0.25 mg/g is expected to be minimal since the proposed clinical use is acute in nature.

Reproductive toxicology: In the original NDA review, the sponsor submitted a Segment II reproductive toxicology study in the rat with the 1:1 combination of **lidocaine:prilocaine**. Additional arms included a high dose of each compound administered alone. The lidocaine/prilocaine formulation produced no embryo-fetal developmental effects at subcutaneous doses up to 40 mg/kg each. Similarly, lidocaine (up to 30 mg/kg SC) and prilocaine (up to 300 mg/kg, IM) alone produced no fetal effects; prilocaine also had no effect on fertility. To complete the reproductive toxicology battery the sponsor submitted studies conducted by ——— in support of the original Lidocaine (Xylocaine) and Prilocaine (Citanest) NDAs.

Segment II studies for **lidocaine** were completed in the rat and rabbit models. Treatment of male rats with lidocaine (30 mg/kg, s.c.; 180 mg/m^2, approximately equivalent to the maximum recommended human dose per session assuming 100% bioavailability) for 9 weeks prior to mating did not alter the fertility of male rats. Likewise, treatment of female rats with 30 mg/kg, s.c. lidocaine for 2 weeks prior to mating through day 14 of pregnancy did not produce any alterations in reproductive performance nor embryonic toxicity. In the rabbit, treatment with **lidocaine** at a dose of 5 mg/kg, s.c. (60 mg/m^2; 0.4-fold the maximum recommended human dose per session assuming 100% bioavailability) from day 6 through 18 of pregnancy did not produce any teratogenic effects. A dose of 15 mg/kg, s.c. (180 mg/m^2; 1.4-fold the maximum recommended human dose per session assuming 100% bioavailability) did not produce evidence of teratogenicity. The non-significant findings of slightly decreased mean fetal body weight and increased minor skeletal abnormalities are suggestive of potential fetotoxicity at this dose.

The sponsor provided data to assess the potential toxic effects of **prilocaine** on embryo-fetal development in the rabbit model. The study was originally completed to test the effects of Citanest-Octapressin (Prilocaine-Vasopressin), a combination drug product (0.033, 0.33, 1.7 ml/kg) on embryonic development. The dose of prilocaine in this study corresponded to 0, 1, 10 and 50 mg/kg, s.c. Female rabbits were treated from day 6 through 18 of pregnancy. There were no effects of drug treatment on the number of implantation sites, litter size, litter and mean pup weight between treatment groups. However, there were several abnormalities noted, including one pup with **spina bifida of a lumbar vertebra**, a major abnormality. The fact that the only observation was in the low-dose group and no other major abnormalities occurred at higher doses supports the conclusion that the finding does not appear to be related to the test article. The sponsor interpreted the finding as a spontaneous event. Retrospective examination of the incidence of spontaneous major malformations detected at the ——— (where the study was conducted) in the New Zealand White Rabbit was 55 cases out of 8036 fetuses. Further, the incidence of spina bifida at this facility was 1 out of 8036 fetuses examined (0.01%). A search of the Historical Control Database of Pre-Clinical Developmental Teratology and Reproductive Toxicity Parameters (Sponsored by ——— detected 1 fetus out of 13820 evaluated to present with the abnormality "External Abnormality: Trunk – Spina Bifida" in rabbits of any strain or stock[2]. The low incidence of this malformation in the historical databases raised

[2] Search was conducted on December 12, 2003 (http://www.hcd.org/).

significant concern. Since this effect occurred in a low-dose animal and not other neural-tube defects were noted in other animals, the effect does not appear to be treatment-related. As such, although the study was of a combination drug, the exposure to procaine in the study was sufficient to conclude that there was no evidence for prilocaine induced teratogenicity, under the conditions tested.

Studies to address the effects of **lidocaine** on the peri- and postnatal development (Segment III) in rats were conducted via both the subcutaneous and intramuscular route of administration. Rats were treated with lidocaine (0, 1, 5, or 10 mg/kg, s.c) from day 15 of pregnancy to day 10 postparturition (weening). Observations of the litters from the high dose group (10 mg/kg, s.c.; 60 mg/m^2; 0.5-fold the maximum recommended human dose per session assuming 100% bioavailability) detected a slight decrease in litter size and number of litter pups and increased pup loss. In contrast, there were no differences in mean pup weights or time to occurrence of physical developmental milestones or the types/frequencies of gross malformations between groups. However, the high dose also produced evidence of maternal toxicity including decreased weight gain, decreased food consumption and prolongation of the gestation period. There were no adverse effects in either the dams or the pups at the dose of 5 mg/kg, s.c. (30 mg/m^2). A second study was conducted via the intramuscular route of administration. Lidocaine (6 mg/kg, i.m.; 36 mg/m^2, 0.2-fold the maximum recommended human dose per session assuming 100% bioavailability) was bilaterally injected intramuscularly on pregnancy day 10 and 11. Development of the offspring was monitored via tests of spontaneous activity, nociception, learning ability and physical development. Under the conditions of the study, the pups from the lidocaine group were comparable to those from the vehicle group.

Finally, the sponsor provided a report from 1964 where **lidocaine or prilocaine** (10 or 30 mg/kg, s.c.) was administered daily for 8 months to both male and females. A total of three mating periods were obtained and pups were examined for developmental abnormalities at birth and at weaning. Treatment of the F_0 generation with either dose of lidocaine or prilocaine did not alter the number of litters produced, the mean number of pups born per litter, the mean weight of pups at birth and the weaning or the distribution of sex among pups. However, treatment with either dose of lidocaine or prilocaine (10 or 30 mg/kg, s.c.) produced a significant decrease in the average number of pups per litter surviving until weaning. The study concludes that neither lidocaine nor prilocaine altered the reproductive potential of the rat. Technically, this study does not fully address the post-natal development effects of prilocaine or lidocaine, since f the F_1 generation was not tested for reproductive capacity, behavioral testing or reflex testing.

Special toxicology: There were no special toxicology studies completed for this NDA round. The local toxicity of lidocaine and prilocaine dental gel (2.5%:2.5%; doses of 25-50 mg/kg; 1-2 hours exposure) was examined in the anesthetized dog model. There was no evidence of local irritation noted following exposure of the left gingival sulcus of the lower jaw or the buccal gingival parallel to the first application. This was a 5-day study will tissue exposure for 1-2 h every other day. The local tissue irritation potential was

also examined with the lidocaine prilocaine cream as described in the review for NDA 19-941.

3.4.2 Single-dose toxicity

Single-dose toxicity studies were not included in this submission. Acute toxicology studies were completed with the combination of lidocaine and prilocaine in the male mouse and rat via the intravenous route of administration. In addition the sponsor completed an acute subcutaneous toxicology study for both compounds and EMLA cream in the male rats. Finally, an acute dermal toxicology study in the rabbit was completed with EMLA cream. These studies were reviewed for NDA 19-941 (EMLA Cream). For this IND/NDA, the sponsor also completed single dose oral gavage study in rats for each compound. According to the original NDA review for Oraqix®, "Newly conducted acute toxicity studies in rats confirmed that lidocaine and prilocaine effects are primarily CNS-related and extremely high doses can induce lethality. In previously conducted studies, administration of a lidocaine/prilocaine dental gel resulted in no local toxicity, while immobility or pronounced lethargy, labored respiration, dyspnea, cyanosis and convulsions were observed with intravenous or subcutaneous administration. No local toxicity was observed following rectal or dermal application."

3.4.3 Repeat-dose toxicity

Repeat-dose toxicology studies consisted of a 1-month rectal PK/toxicology study of EMLA cream in dogs. There were no other repeat-dose toxicology studies conducted for either lidocaine or prilocaine.

3.4.4. Genetic toxicology

Study title: **Mouse micronucleus test for prilocaine** (NOTE: This study was previously reviewed by Dr. Kathleen Haberny).

Key findings: The sponsor noted that the doses chosen for the mouse micronucleus test conducted in 1988 and reported in the initial IND were based on dose range finding studies that preceded the micronucleus test and not routinely reported. In addition, clinical observations were not reported in 1988 and therefore those observations are reported here. The sponsor maintains that based upon the range-finding assay, the high dose of 400 mg/kg does appear to be the maximum tolerated dose. Therefore, the conclusions of the original report are valid, i.e., that prilocaine tested negative in the *in vivo* mouse micronucleus assay. The documentation below includes the original review by Dr. Kathleen Haberny as well as the amendment to the original study report defining the dose selection. If the males and females are examined together, the 400 mg/kg dose appears to be the maximum tolerated dose in the mouse model.

Study no.: 87055 (Document No. T1968-02)

Volume #, and page #: Volume 3 of 3 (N000 B2)
Conducting laboratory and location: AstraZeneca Research and Development Södertälje, Sweden
Date of study initiation: August 1987
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Prilocaine, Lot# 325-1, purity [redacted]

Methods

Strains/species/cell line: NMRI mouse

Doses used in definitive study: 779 and 1558 µmol/kg (200 and 400 mg/kg); this dose was intended to be close to the MTD (20 ml/kg). Doses were administered via the subcutaneous route of administration.

Basis of dose selection: Although not reported in the original NDA submission or the original study report from 1988, AstraZeneca has determined that dosing was based on a dose-range finding assay conducted prior to the *in vivo* chromosome aberrations assay. The treatment groups in this dose-range finding study are described by the sponsor's table below:

Treatment	Dose		Concentration		Dose volume	No. of animals	
	µmol/kg	mg/kg	µmol/mL	mg/mL	mL/kg	(M)	(F)
Untreated	0	0	0	0	0	1	0
Prilocaine HCl	1500	400	76	20	20	4	4
Prilocaine HCl	1900	500	95	25	20	4	4
Prilocaine HCl	2300	600	110	30	20	4	4
Prilocaine HCl	3000	800	150	40	20	4	4

Animal observations for the above study were collected, but not reported in the report submitted with the original NDA submission. In the dose-range finding study, at 400 mg/kg, animals were sedated 10-15 minutes after treatment. After about 1.5 hours, 2 males showed tonic clonic convulsions and two males were still sedated. One female animal started to move 2 hours after dosing but the three other females were still sedated. Animals began to recover 4 hours after dosing.

Following 500 mg/kg, one male died during the night.

Following 600 mg/kg, two males died 1.5 hours and 4 hours after dosing. The other two males were sedated. One female died 40 minutes after dosing, the others were sedated.

Following 800 mg/kg, all animals showed clonic convulsions approximately 10 minutes after dosing. Two males and all 4 females died 20 minutes to 2.5 hours after dosing. Two males survived but were still sedated 4 hours after dosing.

Summary of animal observations in the dose-range finding study:

	Males					Females				
Dose	**0**	**400**	**500**	**600**	**800**	**0**	**400**	**500**	**600**	**800**
Mortality	0/1	0/4	1/4	2/4	2/4	0/0	0/4	0/4	1/4	4/4
Convulsions	0/1	2/4	?	4/4	4/4	0/0	0/4	?	?	4/4
Sedation	0/1	4/4	?	4/4	4/4	0/0	4/4	?	4/4	4/4

Based upon the results of dose-range finding study, AstraZeneca determined that the maximum tolerated dose was determined to be 400 mg/kg.

Negative controls: Sterile water vehicle, physiological saline.

Positive controls: methyl methanesulfonate (MMS) dissolved in sterile water (455 μmol/kg).

Incubation and sampling times: Five males and females per dose group (0, 200 or 400 mg/kg) were killed by cervical dislocation 24, 48 and 72 hours after SC administration of test compound. Positive control animals were killed 24 hours after administration. Femoral bone marrow was aspirated and dispersed in a mixture of fetal calf serum and phosphate buffer and smears were made. Slides were coded and examined by light microscopy. The ratio of PCE to all erythrocytes was determined from the first 1000 erythrocytes examined. The frequency of micronucleated cells among both types of erythrocytes was registered concurrently. Altogether, 1000 PCE with and without micronuclei were scored from each animal. The mean incidence of micronucleated PCEs and the ratio of polychromatic to all erythrocytes in treated and positive control groups were compared with the corresponding data from negative control groups. Kruskal-Wallis mean rank test was performed.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The original study appears to be a valid assay for the following reasons: 1) the positive controls were appropriate and produced a clear statistically significant increase in the % of polychromatic cells, the high dose used in the males (400 mg/kg) appears to be acceptable as the maximum tolerated dose based upon the mortality of one of four males in the 500 mg/kg group.

Study outcome: Animal observations recorded during the study indicate that at the high dose level, animals were "severely affected" 2 hours after dosing, but started to recover 3 hours after dosing. The animals in the low dose group started to recover 2.5 hours after dosing. However, the animal observations for the definitive study do not describe what

"severely affected" meant. The results of the study indicate that under the conditions of the assay, prilocaine was not clastogenic. The study results are summarized in the sponsor's table reproduced below. Based upon the data, MMS, the positive control produced a significant increase in the incident of micronucleated polychromatic erythrocytes (PCE) and the % ratio of PCE to total erythrocytes counted (PCE+NCE) suggesting that MMS was clastogenic in this assay and produced evidence of bone marrow suppression. Prilocaine treatment of the mice at doses up to 400 mg/kg did not produce an increase in the incidence of micronucleated polychromatic erythrocytes (PCE). Under the conditions tested, MMS produced a significant suppression of the bone marrow, however at 72 hours, prilocaine, if anything, statistically stimulated the bone marrow.

SUMMARY OF ALL RESULTS

Test compound	Kill time	No. of animals		Dose	Incidence MPCE	PCE / PCE+NCE	Incidence MNCE
	h	M	F	umol/kg	o/oo	%	o/oo
0.9% NaCl	24	5	5	0	1.7	43.9	0.9
Prilocaine	24	5	5	779	2.3	49.6	1.6
	24	5	5	1558	2.8	49.1	1.4
MMS	24	5	5	455	58.2***	36.6*	1.6
0.9% NaCl	48	5	5	0	1.6	45.2	0.7
Prilocaine	48	5	5	779	1.8	42.9	0.7
	48	5	5	1558	2.0	45.4	1.6
0.9% NaCl	72	5	5	0	2.0	42.1	0.9
Prilocaine	72	5	5	779	1.9	54.9**	0.9
	72	5	5	1558	2.3	51.3	1.2

The ICH Guidance S2B, "[t]he dose range-finding study should (i) give information on the shape of the toxicity dose response curve if the test compound exhibits toxicity, (ii) include highly toxic concentrations, and (iii) include quantification of mutants in the cytotoxic range. If a compound is not toxic, then mutants should nevertheless be quantified." Based upon the additional details from the dose range finding study, the 400 mg/kg dose of prilocaine can be considered to be or even exceed the maximum tolerated dose in males. The maximum tolerated dose in females, however, appears to be defined by sedation induced by prilocaine injections. Safety pharmacology studies indicated that secondary pharmacological effects include CNS stimulation followed by depression which can lead to respiratory arrest and death at higher doses. Given the evidence for prolonged sedation with both 200 and 400 mg/kg in the definitive study, and the results of acute toxicology studies the choice of 400 mg/kg appears to adequately characterize the top dose for further study.

Study title: Mouse micronucleus test of lidocaine hydrochloride monohydrate (LEA152)

Key findings: This study was originally reviewed for NDA 19-941 (EMLA cream) and determined to be acceptable. The sponsor amended the study report in 2003 to include the results of three range finding assays. Based upon the animal observations, this reviewer concurs with the original review of the study in NDA 19-941. The results indicate that lidocaine was not clastogenic in the *in vivo* mouse micronucleus assay, under the conditions tested.

Study no.:	Original T2362, Amendment 1
Volume #, and page #:	Volume 3 of 3; page 55
Conducting laboratory and location:	AstraZeneca R&D Södertälje, Sweden
Date of study initiation:	Original study March 12, 1991
GLP compliance:	Yes
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	Batch 142-1, [redacted], purity.

Methods

Strains/species/cell line: NMRI mouse, age range of 8-9 weeks.

Doses used in definitive study: Doses of 75 and 150 mg/kg, s.c. were chosen for the definitive study based upon preliminary dose range finding studies described below.

Basis of dose selection: Three range finding studies were conducted to determine the dose of lidocaine to be used in this study. The dose-range finding studies were designed as described in the three tables below:

Range finding test 1

In the range finding test 1, male and female mice were dosed subcutaneously according to the following table:

Treatment	Dose		Concentration		Dose volume	No. of animals	
	µmol/kg	mg/kg	µmol/mL	mg/mL	mL/kg	(M)	(F)
Lidocaine HCl H_2O	700	200	35	10	20	2	4
Lidocaine HCl H_2O	1000	300	52	15	20	2	2
Lidocaine HCl H_2O	1400	400	70	20	20	2	2
Lidocaine HCl H_2O	2100	600	100	30	20	2	2

Range finding test 2

In the range finding test 2, male and female mice were dosed subcutaneously according to the following table:

Treatment	Dose		Concentration		Dose volume	No. of animals	
	µmol/kg	mg/kg	µmol/mL	mg/mL	mL/kg	(M)	(F)
Untreated	0	0	0	0	0	7	4
NaCl 9 mg/ml	0	0	0	0	20	6	6
Lidocaine HCl H_2O	350	100	17	5.0	20	6	6
Lidocaine HCl H_2O	690	200	35	10	20	6	6
MMS	450	50	23	2.5	20	5	5

Range finding test 3

In the range finding test 3, male and female mice were dosed subcutaneously according to the following table:

Treatment	Dose		Concentration		Dose volume	No. of animals	
	µmol/kg	mg/kg	µmol/mL	mg/mL	mL/kg	(M)	(F)
Lidocaine HCl H_2O	520	150	26	7.5	20	6*	5
Lidocaine HCl H_2O	690	200	35	10	20	6*	6*

* 1 animal not dosed correctly

Animal observations are summarized in the table below:

Summary of animal observations in the dose range finding studies:

	Males and Females Combined						
Dose	0	100	150	200	300	400	600

Mortality	0/23	0/12	0/11	2/30	1/4	2/4	3/4

On the basis of the above mortality findings, the dose of 150 mg/kg was chosen as the maximum tolerated dose for the micronucleus assay. There were no additional clinical observations noted in this study.

Negative controls: Physiological saline.

Positive controls: Methyl methanesulfonate (MMS) was used as the positive control at a concentration of 23 μmol/ml.

Incubation and sampling times: Animals were sacrificed either 24, 48 or 72 hours after drug administration. The positive control animals were sacrificed 24 hours after drug administration.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): Consistent with the original reviewer of NDA 19-941, the study appears to be valid since the positive control produced a clear increase in the number of micronucleated erythrocytes, the time points examined were appropriate and the doses tested included a maximally tolerated dose based upon increased mortality at the higher dose tested.

Study outcome: Under the conditions of the assay, lidocaine did not cause any significant increase in the incidence of micronucleated polychromatic erythrocytes at any of the three sampling times (24, 48 or 72 hours). In contrast, MMS produced a significant increase in the incidence of micronucleated polychromatic erythrocytes. A summary of the results are reproduced below from the sponsor's submission:

Test compound	Sampling time	No. of animals		Dose	Incidence MPCE	PCE / PCE+NCE	Incidence MNCE
	h	M	F	μmol/kg	o/oo	%	o/oo
0.9% NaCl	24	5	5	0	1.7	65.5	0.9
Lidocaine HCl H_2O	24	5	5	260	1.4	66.8	0.0
Lidocaine HCl H_2O	24	5	5	519	1.2	60.7	0.6
MMS	24	5	5	484	23.6***	58.3	0.6
0.9% NaCl	48	5	5	0	0.8	54.6	0.0
Lidocaine HCl H_2O	48	5	5	260	1.1	48.7	1.1
Lidocaine HCl H_2O	48	5	5	519	0.8	47.6	0.6
0.9% NaCl	72	5	5	0	0.8	50.1	0.8
Lidocaine HCl H_2O	72	5	5	260	1.1	47.3	0.6
Lidocaine HCl H_2O	72	5	5	519	0.7	52.5	0.6

As indicated in the table above, MMS produced a clear increase in the incidence of MPCEs. Under the conditions of the assay, lidocaine was not clastogenic at any time point.

Study title: Chromosomal aberrations in cultured human peripheral blood lymphocytes

Key findings: Prilocaine hydrochloride was considered negative for inducing structural chromosomal aberrations in cultured human peripheral blood lymphocytes with and without metabolic activation.

Study no.:	25022-0-449OECD
Volume #, and page #:	N 000 B2, page 3
Conducting laboratory and location:	
Date of study initiation:	April 14, 2003
GLP compliance:	Yes
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	Prilocaine hydrochloride, Batch No. 6010, Purity ___

Methods:

Strains/species/cell line: Cultured human peripheral blood lymphocytes. Cells were stimulated to divide by exposure to the mitogen phytohemagglutinin (PHA).

Doses used in definitive study: In assays with metabolic activation, the concentrations of 3.63, 5.17, 7.40 and 10.6 mM were analyzed. In the confirmatory assay without metabolic activation, concentrations of 0.245, 0.489, 0.979 and 1.96 mM were analyzed. In the confirmatory assay with metabolic activation, concentrations of 3.92, 5.87, 7.83 and 10.6 mM were analyzed. The table below shows the concentrations runs in the confirmatory assays.

Without metabolic activation

Prilocaine HCl (µg/mL)	62.5	125	250	500	1000	1500	2000	2350	2700
Prilocaine HCl (mM)	0.245	0.489	0.979	1.96	3.92	5.87	7.83	9.20	10.6
Prilocaine base (µg/mL)	53.9	108	216	431	863	1290	1730	2030	2330

With metabolic activation

Prilocaine HCl (µg/mL)	500	1000	1500	2000	2700
Prilocaine HCl (mM)	1.96	3.92	5.87	7.83	10.6
Prilocaine base (µg/mL)	431	863	1290	1730	2330

Basis of dose selection: Solubility and cytotoxicity were evaluated for prilocaine. In cell culture grade water, prilocaine hydrochloride is soluble at a concentration of 52.0 mg/ml (0.204 M). When added to culture media to produce a concentration of 2600 µg/ml there is no precipitate or change in color noted (pH was 7.5=culture medium alone).

The following concentrations were tested with a ~3-hour treatment and a ~22-hour harvest in the initial chromosomal aberrations assays with and without metabolic activation:

Prilocaine HCl (µg/mL)	18.3	26.2	37.4	53.4	76.3	109	156	222	318	454	648	926	1320	1890	2700
Prilocaine HCl (mM)	0.0716	0.103	0.146	0.209	0.299	0.427	0.611	0.869	1.25	1.78	2.54	3.63	5.17	7.40	10.6
Prilocaine base (µg/mL)	15.8	22.6	32.3	46.1	65.8	94.0	135	191	274	392	559	799	1140	1630	2330

In the assay without metabolic activation, the test article produced a concentration dependent reduction in the mitotic index at concentrations of 0.245 to 10.6 mM. In the assay with metabolic activation, there was no reduction in the mitotic index of the cultures treated with 10.6 mM of prilocaine base compared to vehicle controls.

Negative controls: Negative controls consisted of cells in culture media alone. Vehicle controls were cultures containing the vehicle for the test article (water at 50 µl/ml). In the activated cultures, the negative and vehicle controls also contained S9 activation mix.

Positive controls: The positive control for the nonactivated system was mitomycin C (MMC). The positive control for the activated system was cyclophosphamide (CP). Both were dissolved in sterile deionized water.

Incubation and sampling times: In the initial chromosomal aberrations assay, cultures were incubated for 3 hours in the presence of test article, vehicle control or positive controls with or without the S9 mixture. The cultures were washed with phosphate buffered saline (PBS). The cultures were then re-fed with the culture medium and incubated for the rest of the culture period (total incubation time ~22 hours). For the confirmatory assay, cells were cultured with the test article for a total of 22 hours without metabolic activation. For the activated cultures, cultures were treated for 3 hours, washed and returned to culture for the remaining time (total culture time ~22 hrs).

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The study appears to be valid, as the highest concentration tested was 10 mM, the maximum required for nontoxic compounds according to ICH S2A and OECD guidance, the positive controls were appropriate for the conditions of the assay, produced clear responses and the protocol appears to be consistent with OECD guidelines.

Study outcome: In the initial chromosomal aberrations assay without metabolic activation, prilocaine was tested up to the limit concentration of the drug (10 mM). Under these conditions, there was only a 28% reduction in mitotic index as indicated in the sponsor's table 1 below:

Table 1: Assessment of Toxicity for Chromosomal Aberrations Assay - Without Metabolic Activation - ~3 Hour Treatment, ~22 Hour Harvest

Assay No.: 25022 Trial No.: B1 Date: 05/01/03 Lab No.: CY042803
Test Article: Prilocaine hydrochloride

Treatment			% Mitotic Index A Culture	% Mitotic Index B Culture	Average % Mitotic Index	% Mitotic Reduction
Negative Control	RPMI 1640		4.1	3.7	3.9	--
Vehicle Control	CCGW	50.00 µL/mL	4.6	3.2	3.9	0
Test Article		5.17 mM	3.8	3.4	3.6	8
		7.40 mM	2.5	3.3	2.9	26
		10.6 mM	1.7	3.9	2.8	28

RPMI 1640 = culture medium
CCGW= cell culture grade water
Doses of 5.17, 7.40, and 10.6 mM correspond to 1140, 1630, and 2330 µg/mL, respectively, of the prilocaine base.

Assessment of the chromosome aberrations at under these conditions produced a negative result for prilocaine, however, the positive control mitomycin C tested positive. The data is reproduced in sponsor's table 2 below:

Genetic Toxicology Assay Number: 25022-0-449OECD

Table 2: Chromosome Aberrations in Human Lymphocytes - Without Metabolic Activation - ~3 Hour Treatment, ~22 Hour Harvest

Assay No.: 25022 Trial No.: B1 Date: 05/01/03 Lab No.: CY042803 Test Article: Prilocaine hydrochloride

			CELLS SCORED	% MITOTIC INDEX REDUCTION [a]	# ENDOREDUPLICATED CELLS	# POLYPLOID CELLS	JUDGEMENT (+/-) [b]	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOME ABERRATIONS: Gaps	Simple Breaks	chte	chre	mab	TOTALS [c] -g	TOTALS [c] +g	JUDGEMENT (+/-) [d]
CONTROLS															
NEGATIVE: RPMI 1640		A	100		0	0			1				1	1	
		B	100		0	0		2					0	2	
		TOTAL	200					2	1				1	3	
		AVERAGE	%	-	0.0	0.0		1.0	0.5				0.5	1.5	
VEHICLE: CCGW	50.0 µL/mL	A	100		0	0			1				1	1	
		B	100		0	0		2					0	2	
		TOTAL	200					2	1				1	3	
		AVERAGE	%	0	0.0	0.0		1.0	0.5				0.5	1.5	
POSITIVE: MMC	1.50 µg/mL	A	63		0	0		4	30	21		3	40	42	
		B	37		0	0		4	8	10		3	16	19	
		TOTAL	100					8	38	31		6	56	61	
		AVERAGE	%	-	0.0	0.0	-	8.0	38.0	31.0		6.0	56.0	61.0	+
TEST ARTICLE	3.63 mM	A	100		0	0		3					0	3	
		B	100		0	0							0	0	
		TOTAL	200					3					0	3	
		AVERAGE	%	-	0.0	0.0	-	1.5					0.0	1.5	-
	5.17 mM	A	100		0	0		1					0	1	
		B	100		0	0							0	0	
		TOTAL	200					1					0	1	
		AVERAGE	%	8	0.0	0.0	-	0.5					0.0	0.5	-
	7.40 mM	A	100		0	0							0	0	
		B	100		0	0		2					0	2	
		TOTAL	200					2					0	2	
		AVERAGE	%	26	0.0	0.0	-	1.0					0.0	1.0	-
	10.6 mM	A	100		0	0		1					0	1	
		B	100		0	1							0	0	
		TOTAL	200					1					0	1	
		AVERAGE	%	28	0.0	0.5	-	0.5					0.0	0.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations

[a] % Mitotic index reduction as compared to the vehicle control.

[b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.

[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640=Culture medium CCGW= cell culture grade water MMC = Mitomycin C

Doses of 926, 1320, 1890, and 2700 µg/mL correspond to 3.63, 5.17, 7.40, and 10.6 mM, respectively, and 799, 1140, 1630, and 2330 µg/mL, respectively, of the prilocaine base.

Under conditions of metabolic activation, prilocaine produced only a 13% reduction in the mitotic index at limit concentration of 10 mM (see sponsor's table 3 below). Therefore the concentrations chosen for scoring were the top four concentrations (3.63, 5.17, 7.40 and 10.6 mM).

Table 3: Chromosome Aberrations in Human Lymphocytes - With Metabolic Activation - ~3 Hour Treatment, ~22 Hour Harvest

Assay No.: 25022 Trial No.: B1 Date: 05/01/03 Lab No.: CY042803
Test Article: Prilocaine hydrochloride

Treatment			% Mitotic Index A Culture	% Mitotic Index B Culture	Average % Mitotic Index	% Mitotic Reduction
Negative Control	RPMI 1640		5.1	6.2	5.7	–
Vehicle Control	CCGW	50.0 µL/mL	5.7	6.6	6.2	0
Test Article		5.17 mM	6.4	6.5	6.5	0
		7.40 mM	5.3	5.9	5.6	10
		10.6 mM	5.7	5.1	5.4	13

RPMI 1640 = culture medium
CCGW = cell culture grade water
Doses of 5.17, 7.40, and 10.6 mM correspond to 1140, 1630, and 2330 µg/mL, respectively, of the prilocaine base..

In the presence of metabolic activation, prilocaine also tested negative for the induction of chromosome aberrations in human lymphocytes. In contrast, cyclophosphamide produced a clear positive response. These data are reproduced in sponsor's table 4 below:

Table 4: Chromosome Aberrations in Human Lymphocytes - With Metabolic Activation - ~3 Hour Treatment, ~22 Hour Harvest

Assay No.: 25022 Trial No.: B1 Date: 05/01/03 Lab No.: CY042803 Test Article: Prilocaine hydrochloride

			CELLS SCORED	% MITOTIC INDEX REDUCTION [a]	# ENDOREDUPLICATED CELLS	# POLYPLOID CELLS	JUDGEMENT (+/-) [b]	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOME ABERRATIONS: Gaps	Simple Breaks	chte	chre	mab	TOTALS [c] -g	TOTALS [c] +g	JUDGEMENT (+/-) [d]
CONTROLS															
NEGATIVE: RPMI 1640		A	100		0	0		1					0	1	
		B	100		0	0		1					0	1	
		TOTAL	200					2					0	2	
		AVERAGE	%	-	0.0	0.0		1.0					0.0	1.0	
VEHICLE: CCGW	50.0µL/mL	A	100		0	0							0	0	
		B	100		0	0		1					0	1	
		TOTAL	200					1					0	1	
		AVERAGE	%	0	0.0	0.0		0.5					0.0	0.5	
POSITIVE: CP	40.0µg/mL	A	50		0	0		7	18	3		1	21	26	
		B	50		0	0		7	20	3			20	23	
		TOTAL	100					14	38	6		1	41	49	
		AVERAGE	%	-	0.0	0.0	-	14.0	38.0	6.0		1.0	41.0	49.0	+
TEST ARTICLE	3.63mM	A	100		0	0		2					0	2	
		B	100		0	0							0	0	
		TOTAL	200					2					0	2	
		AVERAGE	%	-	0.0	0.0	-	1.0					0.0	1.0	-
	5.17mM	A	100		0	0		1					0	1	
		B	100		0	0							0	0	
		TOTAL	200					1					0	1	
		AVERAGE	%	0	0.0	0.0	-	0.5					0.0	0.5	-
	7.40mM	A	100		0	1							0	0	
		B	100		0	0							0	0	
		TOTAL	200										0	0	
		AVERAGE	%	10	0.0	0.5	-						0.0	0.0	-
	10.6mM	A	100		0	1		1					0	1	
		B	100		0	2		2					0	2	
		TOTAL	200					3					0	3	
		AVERAGE	%	13	0.0	1.5	-	1.5					0.0	1.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations

[a] % Mitotic index reduction as compared to the vehicle control.

[b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.

[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640= culture medium CCGW = cell culture grade water CP = Cyclophosphamide

Doses of 3.63, 5.17, 7.40, and 10.6 mM correspond to 559, 799, 1140, 1630, and 2330 µg/mL, respectively, of the prilocaine base.

The above findings were tested in a confirmatory assay both with and without metabolic activation. Incubation of human lymphocytes with prilocaine in the absence of metabolic activation for approximately 22 hours produced a greater than 50% reduction in mitotic index at concentrations of 1.96 mM and above (see sponsor's table 5 below).

Table 5: Assessment of Toxicity for Chromosomal Aberrations Assay - Without Metabolic Activation - ~22 Hour Treatment, ~22 Hour Harvest

Assay No.:25022 Trial No.: C1 Date: 05/29/03 Lab No.: CY060203
Test Article: Prilocaine hydrochloride

Treatment			% Mitotic Index A Culture	% Mitotic Index B Culture	Average % Mitotic Index	% Mitotic Reduction
Negative Control	RPMI 1640		5.8	7.0	6.4	--
Vehicle Control	CCGW	50.0 µL/mL	6.5	6.2	6.4	0
Test Article		0.245 mM	6.0	5.4	5.7	11
		0.489 mM	4.4	5.5	5.0	22
		0.979 mM	4.4	5.3	4.9	23
		1.96 mM	1.8	2.2	2.0	69
		3.92 mM	1.2	1.3	1.3	80
		5.87 mM	1.2	0.9	1.1	83
		7.83 mM	0.3	0.6	0.5	92
		9.20 mM	0.2	0.3	0.3	95
		10.6 mM	0.0	0.1	0.1	98

RPMI 1640 = culture medium
CCGW = cell culture grade water
Doses of 0.245, 0.489, 0.979, 1.96, 3.92, 5.87, 7.83, 9.20, and 10.6 mM correspond to 53.9, 108, 216, 431, 863, 1290, 1730, 2030, and 2330 µg/mL, respectively, of the prilocaine base.

As such, the concentrations scored for chromosome aberrations were 0.245, 0.489, 0.979 and 1.96 mM. Under these conditions, prilocaine tested negative for chromosome aberrations in the absence of metabolic activation, as depicted in sponsor's table 6 below:

Table 6: Chromosome Aberrations in Human Lymphocytes - Without Metabolic Activation - ~22 Hour Treatment, ~22 Hour Harvest

Assay No.: 25022 Trial No.: C1 Date: 05/29/03 Lab No.: CY060203 Test Article: Prilocaine hydrochloride

			CELLS SCORED	% MITOTIC INDEX REDUC-TION[a]	# ENDO-REDUPLI-CATED CELLS	# POLY-PLOID CELLS	JUDGE-MENT (+/-)[b]	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOME ABERRATIONS: Gaps	Simple Breaks	chte	chre	mab	TOTALS[c] -g	TOTALS[c] +g	JUDGE-MENT (+/-)[d]
CONTROLS															
NEGATIVE: RPMI 1640		A	100		0	0		2	1				1	3	
		B	100		0	0							0	0	
		TOTAL	200					2	1				1	3	
		AVERAGE	%	-	0.0	0.0		1.0	0.5				0.5	1.5	
VEHICLE: CCGW	50.0µL/mL	A	100		0	0		1	1				1	2	
		B	100		0	0		1					0	1	
		TOTAL	200					2	1				1	3	
		AVERAGE	%	0	0.0	0.0		1.0	0.5				0.5	1.5	
POSITIVE: MMC	0.300µg/mL[e]	A	63		0	0		6	12	7	1		18	19	
		B	18		0	0			5	1			6	6	
		TOTAL	81					6	17	8	1		24	25	
		AVERAGE	%	-	0.0	0.0	-	7.4	21.0	9.9	1.2		29.6	30.9	+
TEST ARTICLE	0.245mM	A	100		0	0							0	0	
		B	100		0	0							0	0	
		TOTAL	200										0	0	
		AVERAGE	%	11	0.0	0.0	-						0.0	0.0	-
	0.489mM	A	100		0	0							0	0	
		B	100		0	0		1	1				1	2	
		TOTAL	200					1	1				1	2	
		AVERAGE	%	22	0.0	0.0	-	0.5	0.5				0.5	1.0	-
	0.979mM	A	100		0	0		1	2				2	3	
		B	100		0	0							0	0	
		TOTAL	200					1	2				2	3	
		AVERAGE	%	23	0.0	0.0	-	0.5	1.0				1.0	1.5	-
	1.96mM	A	100		0	0		1	1				1	2	
		B	100		0	0							0	0	
		TOTAL	200					1	1				1	2	
		AVERAGE	%	69	0.0	0.0	-	0.5	0.5				0.5	1.0	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations
[a] % Mitotic index reduction as compared to the vehicle control.
[b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.
[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.
[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640= culture medium CCGW = cell culture grade water MMC = Mitomycin C
[e] Only 10 metaphase cells from culture B were analyzed for polyploidy and endoreduplication
Doses of 0.245, 0.489, 0.979, and 1.96 mM correspond to 53.9, 108, 216, and 431 µg/mL, respectively, of the prilocaine base.

In the presence of metabolic activation, prilocaine did not reduce the mitotic index at concentrations as high as 11 mM. As such the concentrations chosen for scoring were 3.92, 5.87, 7.83 and 10.6 mM. As depicted in sponsor's table 8 reproduced below, under conditions of metabolic activation, prilocaine tested negative in the confirmatory assay. In contrast, cyclophosphamide treatment produced a clear positive result.

Table 8: Chromosome Aberrations in Human Lymphocytes - With Metabolic Activation - ~3 Hour Treatment, ~22 Hour Harvest

Assay No.: 25022 Trial No.: C1 Date: 05/29/03 Lab No.: CY060203 Test Article: Prilocaine hydrochloride

			CELLS SCORED	% MITOTIC INDEX REDUCTION[a]	# ENDOREDUPLICATED CELLS	# POLYPLOID CELLS	JUDGEMENT (+/-)[b]	NUMBERS AND PERCENTAGES (%) OF CELLS SHOWING STRUCTURAL CHROMOSOME ABERRATIONS: Gaps	Simple Breaks	chte	chre	mab	TOTALS[c] -g	TOTALS[c] +g	JUDGEMENT (+/-)[d]
CONTROLS															
NEGATIVE: RPMI 1640		A	100		0	0			1				1	1	
		B	100		0	1							0	0	
		TOTAL	200						1				1	1	
		AVERAGE	%	-	0.0	0.5			0.5				0.5	0.5	
VEHICLE: CCGW	50.0µL/mL	A	100		0	0		1					0	1	
		B	100		0	0							0	0	
		TOTAL	200					1					0	1	
		AVERAGE	%	0	0.0	0.0		0.5					0.0	0.5	
POSITIVE: CP	25.0µg/mL[e]	A	50		0	0		3	19	4			20	21	
		B	50		0	0		4	13	1		1	15	17	
		TOTAL	100					7	32	5		1	35	38	
		AVERAGE	%	-	0.0	0.0	-	7.0	32.0	5.0		1.0	35.0	38.0	+
TEST ARTICLE	3.92mM	A	100		0	0		1					0	1	
		B	100		0	0							0	0	
		TOTAL	200					1					0	1	
		AVERAGE	%	-	0.0	0.0	-	0.5					0.0	0.5	-
	5.87mM	A	100		0	0				1			1	1	
		B	100		0	0		1					0	1	
		TOTAL	200					1		1			1	2	
		AVERAGE	%	-	0.0	0.0	-	0.5		0.5			0.5	1.0	-
	7.83mM	A	100		0	0		1					0	1	
		B	100		0	1			1				1	1	
		TOTAL	200					1	1				1	2	
		AVERAGE	%	-	0.0	0.5	-	0.5	0.5				0.5	1.0	-
	10.6mM[f]	A	100		0	0							0	0	
		B	100		0	1							0	0	
		TOTAL	100										0	0	
		AVERAGE	%	0	0.0	0.5	-						0.0	0.0	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations

[a] % Mitotic index reduction as compared to the vehicle control. [b] Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.

[c] -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.

[d] Significantly greater in -g than the vehicle control, $p \leq 0.01$.

[e] Only 52 metaphase cells from the A culture and 66 metaphase cells from the B culture were analyzed for polyploidy and endoreduplication

[f] Only 89 metaphase cells from the B culture were analyzed for polyploidy and endoreduplication.

RPMI 1640= culture medium CCGW= cell culture grade water CP= cyclophosphamide

Doses of to 3.92, 5.87, 7.83, and 10.6 mM correspond to 863, 1290, 1730, and 2330 µg/mL, respectively, of the prilocaine base.

3.4.5. Carcinogenicity

No additional carcinogenicity data was provided for NDA submission N000 B2 dated June 19, 2003 or N000 B3 dated September 17, 2003. Due to the acute duration of treatment for the given indication, carcinogenicity assessment for this drug product is not required.

3.4.6. Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Effects upon fertility and general reproductive performance in rats of xylocaine given subcutaneously

Key study findings: The effect of lidocaine (0, 3, 10 or 30 mg/kg, s.c.) on the fertility and reproductive performance of Sprague Dawley rats was examined via a study design

comparable to current state of the art with a few differences. The key findings were as follows:

1. Overall, the results of the study suggest that lidocaine treatment of males and females in a Segment I reproductive toxicology study does not produce alterations in the fertility of the parent animals or embryonic toxicity in the pups, under the conditions tested (however, sperm analysis was not conducted in this study).
2. Clinical signs in the F_0 males and females included induration at the site of injection and isolated seizures in two different males treated with the high dose of lidocaine. In contrast, several high dose females demonstrated decreased motor activity and respiratory distress following the test article injection. As such, dosing appears to have produced some evidence of toxicity for study validation.
3. Based upon the study results, the apparent NOAEL for male and female fertility was 30 mg/kg (180 mg/m^2 based on body surface area comparison).

Study no.:	79054 (Document T1593)
Volume #, and page #:	Volume 3 of 3, Page 89
Conducting laboratory and location:	Astra Toxicology Laboratories Södertälje, Sweden
Date of study initiation:	July 2, 1979 (start of dosing)
GLP compliance:	Yes
QA reports:	yes (x) no ( )
Drug, lot #, and % purity:	Lidocaine hydrochloride monohydrate, batch # 1069,

Methods: For the fertility study, male animals were dosed once a day for 9 weeks prior to mating, during mating and subsequently until the results from the mated females sacrificed on day 14 of pregnancy were evaluated. Female rats were dosed for 2 weeks prior to mating, during mating, pregnancy and lactation, up to 20 days post parturition. Half of the females were sacrificed on day 14 of pregnancy and the other half on day 21 post partum.

Doses: 0, 3, 10 and 30 mg/kg lidocaine. Control animals received a saline injection.

Species/strain: Sprague-Dawley rats

Number/sex/group: 15 males and 30 females per group

Route, formulation, volume, and infusion rate: Test article was administered via the subcutaneous route in a volume of 0.3 to 3.0 ml, as indicated in the table below from the sponsor's study report. The formulation of the lidocaine contained 10.0 mg lidocaine, 1 mg methyl parahydroxybenzoate, sodium chloride 6 mg, sodium hydroxide and water.

Satellite groups used for toxicokinetics: None.

Study design: Dosing was selected in light of the proposed human dosage and results obtained in earlier rat studies. Animals were dosed with 0, 3, 10, or 30 mg/kg of lidocaine

Group number	Number and sex	Animal reference number	Daily dose of Xylocain® µmol/kg	mg/kg	Volume ml/kg
1	15 M	1365/79-1379/79	0	0	3.0
	30 F	1380/79-1409/79	0	0	3.0
2	15 M	1410/79-1424/79	10.4	3	0.3
	30 F	1425/79-1454/79	10.4	3	0.3
3	15 M	1455/79-1469/79	34.6	10	1.0
	30 F	1470/79-1499/79	34.6	10	1.0
4	15 M	1500/79-1514/79	103.9	30	3.0
	30 F	1515/79-1544/79	103.9	30	3.0

Parameters and endpoints evaluated: Clinical signs, food consumption, body weights, gestation period, parturition, nursing and lactation were monitored in the parent animals. Terminal investigations included examination of the uterine contents and the following were recorded: number of corpora lutea, total number of implantations, number of viable fetuses, number of dead fetuses, number of resorption sites, and fetal abnormalities (visible external). A gross examination of the abdominal and thoracic cavities of the dams was also completed. Males were sacrificed following evaluation of the females sacrificed on day 14 and discarded without further analysis. The remaining females were allowed to mate and produce litters normally. The litters were examined for litter size, stillborn and viable pups and gross abnormalities. Litter weights were determined at delivery, on Day 7 and Day 21 post partum. Pup survival was monitored daily until Day 21 when they were sacrificed and examined for external and internal abnormalities. The Dams were also sacrificed on Day 21 and the thoracic and abdominal cavities were examined macroscopically for abnormalities.

Results

Mortality: There were no mortalities in either the male or female animals in any group.

Clinical signs: Clinical signs in the F1 males included an observed convulsion in two high-dose males which were noted at 2 weeks and 6 weeks of dosing. A number of males showed dose-related signs of induration of the tissue at the site of injection. This was also noted in female animals in a dose-related manner. Females in the high dose group demonstrated decreased motor activity and signs of respiratory distress following dosing. Specific incidence was not noted in the study report.

Body weight: There were no differences in body weight noted between any groups (male or females).

Food consumption: There were no differences in food consumption in males throughout the dosing period. Food consumption in the high dose female animals was slightly reduced during the last two weeks post-parturition. There were no other differences in

food consumption noted between groups. The decrease in food consumption in the high dose females correlated with small litter size compared to the control group.

Toxicokinetics: Not completed.

Necropsy: Overall, there were no statistically significant differences in the mean total litter size. There was a slightly higher cumulative postnatal loss noted in the high dose females, probably due to the slightly higher loss noted at birth. These changes, however, were not statistically significant. There were no differences noted in mean litter weight (not related to mean litter size) nor mean pup weight compared to controls for any treatment group.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.): There were no differences in the mating performance of females, the length of the gestation period or disturbances in parturition, nursing or lactation. Although there was a slight increase in the mean pre-implantation loss in the mid dose group compared to control, this effect did not reach statistical significance. Likewise, there was a slight decrease in the number of viable embryos in the mid dose group compared to controls which correlated with a slight (non-significant) increase in post-implantation loss. These effects were neither statistically significant nor dose-related and therefore are unlikely to be attributable to the test article.

The study report concludes that there were no obvious adverse effects of lidocaine on fertility and general reproductive performance in female rats, under the conditions tested. In males, the high dose produced convulsions in two animals.

There were no alterations in body weights, food consumption, mating performance, gestation period, parturition, nursing or lactation that could be attributed to the test article, according to the sponsor.

There are several differences in this study design compared to current protocol designs as follows. Specifically, 1) There are no toxicokinetic data for the study, 2)The placebo control was not the same as the vehicle (did not contain methyl parahydroxybenzoate (methylparaben), an antifungal agent in the lidocaine formation which is also listed in the CFR 21CFR184.1490 as a GRAS direct food substance. Further studies by FDA laboratories failed to detect evidence of teratogenicity in mice or rats treated orally with methylparaben (5-550 mg/kg/day orally). Therefore, the presence of the methylparaben should not invalidate the study results, and 3) the study did not examine sperm counts in epididymides or testes nor assess sperm viability.

Embryofetal development

Study title: The effects upon pregnancy in rabbits of Xylocaine given subcutaneously

Key study findings: Lidocaine was administered subcutaneously to pregnant female rabbits at doses of 0, 1, 5 or 15 mg/kg from day 6 through 18 of pregnancy and the following key findings were noted:

1. The sponsor concluded that the NOAEL for teratogenicity in rabbits was 5 mg/kg (60 mg/m^2, based on body surface area).
2. Observations in the high dose group suggested evidence of delayed fetal development as manifested as a slight decrease in fetal weights (7%) and increase in minor skeletal anomalies (55%).
3. The study is considered valid for teratogenic assessment due to evidence of some signs of maternal toxicity following treatment with 15 mg/kg. This dose produced decreased food and water intake and reduced fecal output during the last two days of the study.

Study no.:	76100 (Document T 1442)
Volume #, and page #:	Volume 3 of 3; Page 138
Conducting laboratory and location:	Astra Toxicology Laboratories Södertälje, Sweden
Date of study initiation:	November 9, 1976 June 15, 1983 (report date)
GLP compliance:	Unspecified.
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	Lidocaine hydrochloride, Batch 1008, I, purity was recorded as ———

Methods: Test article was administered once a day to pregnant female rabbits during Days 6-18 of pregnancy.

Doses: 0, 1, 5 and 25 mg/kg.

Species/strain: White New Zealand Rabbits.

Number/sex/group: 13 females/group.

Route, formulation, volume, and infusion rate: Subcutaneous route of administration. The lidocaine was dissolved in physiological saline.

Satellite groups used for toxicokinetics: None.

Study design:

Group number	Number of animals	Animal reference numbers	Daily dose mg/kg	Daily dose µmol/kg
1	13	3422/76 - 3434/76	0	0
2	13	3437/76 - 3449/76	1	3.5
3	13	3452/76 - 3464/76	5	17.3
4	13	3467/76 - 3479/76	25	86.6

Parameters and endpoints evaluated: Clinical signs were recorded daily. Food consumption was determined weekly as the difference of food amount offered and the food amount remaining in each cage (mean daily intake per rabbit). Body weights were recorded on days 1, 6, 10, 14, 18, 19, 24 and 28 of pregnancy and group mean body

weights were calculated. On day 29 of pregnancy, rabbits were sacrificed by intravenous infusion of 30% urethane solution and the uterine contents examined for the following: total number of implantations, total number of viable young, number of dead young, number of resorption sites, number of corpora lutea, and body weights of viable young. Embryonic/fetal deaths were classified as early (probably death between days 7-17 of pregnancy), Late (death probably after day 17 of pregnancy) or abortion (aborted tissue found at the daily examination and only implantation scars noted at autopsy). Pups were examined for external and internal abnormalities and skeletal abnormalities following staining with alizarin. Abnormalities were classified as 1) gross malformations (detectable externally), 2) Visceral anomalies (detected at necropsy) or 3) skeletal anomalies (detected by skeletal staining). Variation in ossification of the 5th sternebral segment and presence of an extra (13th) rib were classified skeletal variants.

Results

Mortality (dams): There were no unscheduled mortalities.

Clinical signs (dams): There were no clinical signs noted in either the control group or the low or mid dose groups. One female in the control group aborted early and showed signs of implantation scars in the uterus (although no tissue was found). Six of 13 high dose female rabbits demonstrated decreased food and water intake and fecal output during the last two days of the study. One of the dams aborted on day 28 (all fetuses were dead). Limited autopsies were conducted on day 29 with no treatment-related findings noted.

Body weight (dams): There was a slight decrease in body weight gain in all treatment groups compared to control animals during the first days after initiation of dosing, however, these differences were not significant.

Food consumption (dams): Although there was a slight decrease in mean food consumption in the high dose group near the end of the study, this effect was not significant.

Toxicokinetics: Not completed.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): There were no alterations in reproductive performance noted across treatment groups. Due to the litter loss in one control female and one high dose female, litter size and fetal losses were basically similar across groups. Mean fetal weights were slightly reduced in the high dose group (7%) compared to controls, however this was not statistically significant.

Offspring (malformations, variations, etc.): There were no clear treatment-related alterations in the frequency of gross malformations, visceral anomalies or skeletal anomalies between groups. There was a slight increase in the percent of skeletal anomalies in the high dose group compared to controls (not significant). The skeletal

anomalies noted were skull and sternebral defects. In addition to limb defects, there was reduced ossification of the phalanges in the high dose group compared to the other treatments.

Study title: Effects of Citanest-Octapressin solution on pregnancy of the New Zealand White rabbit.

Key study findings: This study examined the effects of Citanest-Octapressin solution (Prilocaine-vasopressin solution; 0, 0.033, 0.33 and 1.7 ml/kg) on the pregnancy of the rabbit from day 6-18 of pregnancy. One major fetal abnormality was noted in the 0.033 ml/kg treatment group. One pup showed spina bifida affecting the first lumbar vertebra, also lack of central parietal ossification (considered to be a minor variant). The study report indicates that this type of malformation has previously occurred spontaneously and therefore this finding was not considered to be related to treatment. The sponsor concluded that the combination of prilocaine and vasopressin is not teratogenic under the conditions of the assay. However, as the incidence of **spina bifida** in rabbit pups from the conducting laboratory historical database is 1 fetus out of 8036, this is a rather rare finding. As the effect was noted in the low dose group and the was not dose-dependent, the likelihood that it is related to the treatment is very low.

Study no.:
Volume #, and page #: Volume 3 of 3, Page 180
Conducting laboratory and location:

Date of study initiation: Report date: October 17, 1969
GLP compliance: No
QA reports: yes ( ) no (X)
Drug, lot #, and % purity: Citanest-Octapressin solution is a mixture of prilocaine and synthetic vasopressin marketed overseas. The batch tested in this report is SL16 and contained — Citanest and — IE Octapressin.

Methods:

Doses: 0, 0.033, 0.33 and 1.7 ml/kg of Citanest-Octapressin solution
Species/strain: New Zealand White Rabbits
Number/sex/group: 13 pregnant females per dose group
Route, formulation, volume, and infusion rate: Subcutaneous injection
Satellite groups used for toxicokinetics: None
Study design: Animals were dosed once a day with the test article from day 6 to 18 of pregnancy.

Parameters and endpoints evaluated: Clinical signs and body weights were recorded on days 1, 6, 14, 21 and 28. On Day 29, animals were killed by cervical dislocation, dissected and the number and uterine disposition of young and resorption sites and corpora lutea were counted. Viable young were weighed, sexed and examined internally and externally for abnormalities. All young were preserved, cleared and stained for skeletal examination. Resorption sites were classified as early and late.

Abnormalities were classified as either major (rare and/or probably lethal), variant (minor variations from normal that occur relatively frequently).

Results

Mortality (dams): One female each in the mid-dose and the high-dose group was found dead on days 7 and 16, respectively. The mid-dose animal demonstrated anorexia and weight loss during days 1-6 prior to dosing. The autopsy report described the liver as granular with white mottling on the visceral surface and white flecks on the kidneys. The high-dose animal demonstrated anorexia and weight loss during days 1-6, prior to dosing. The weight loss continued throughout dosing during days 6-14. The body of the high-dose animal revealed autolysis at autopsy. Due to the onset of weight loss prior to test article administration, these deaths were not likely directly linked to the drug.

Clinical signs (dams): Animals that received the high-dose of the test solution showed a local reaction around the injection site. There were no clinical signs noted at the low-dose or the mid-dose.

Body weight (dams): Mean body weight gain in the high-dose females was reduced compared to all other treatment groups. Although there was a slight reduction in body weight in the mid-dose group, the effects was not statistically significant.

Food consumption (dams): Data not provided.

Toxicokinetics: Not completed for this study. The sponsor submitted the following article as an estimate of the blood levels of prilocaine (L67) in the rabbit: Åström A, Persson NH, Örtengren B. 1964. The effect of adrenaline on the toxicity and absorptions of L67 (Citanest®) and some other local anesthetics studied in mice and rabbits. Acta Pharmacol Toxicol 21:161-171. It should be noted that the authors represent the Research Laboratories of AB Astra (Södertälje, Sweden). These authors injected rabbits either subcutaneously into the back or submucosally into the buccal fold of the oral cavity with 20 mg/kg of prilocaine (in a 2% solution) and blood samples were obtained by heart puncture 10, 20, 30, 60, 90 and 120 minutes after administration. The results from the subcutaneous study are reproduced in the table below:

Subcutaneous administration		Intra-oral submucosal administration	
Time after injection (min)	Prilocaine level (μg/ml)	Time after injection (min)	Prilocaine level (μg/ml)
		5	5.2, 5.3
10	0.7, 0.9, 1.4	10	2.7, 3.6,
20	1.0, 1.4, 2.3	20	2.6, 2.8
30	0.9, 1.3, 2.0	30	1.5, 1.7
60	0.4, 0.6, 1.2	60	0.7, 1.0
90	0.4, 0.5, 0.7	90	0.3, 0.4
120	0.2, 0.5, 0.6	120	0.2, 0.3

Examination of the data obtained suggest that the same dose of prilocaine into the submucosal oral tissue of the rabbit produces greater system levels of prilocaine over the first 30 minutes than if the drug were injected subcutaneously.

Terminal and necroscopic evaluations:C-section data (implantation sites, pre- and post-implantation loss, etc.): Pregnancy rates were not altered by drug treatment. Although there was a slight though statistically significant increase in pre-implantation losses in the mid-dose group, the effect was within the historic control range for the laboratory and not dose-dependent.

Offspring (malformations, variations, etc.): All litter parameters examined with within the laboratory standard ranges. These changes included implantation sites, litter size, litter and mean pup weight and therefore litter size which was not significant. There were several abnormalities noted in the pups as follows: One pup born to a dam treated with the low dose presented with **spina bifida** involving the first lumbar vertebra and lacked central parietal ossification (minor variant). According to the study report, this malformation has previously been observed to occur spontaneously. The incidence of minor anomalies were not dose related and within the historical control range. These included: Higher incidence of 13-ribbed pups at all doses of the solution and a higher percentage of 12-ribbed pups showing reduced or unossified sternebrae at the low dose. There were no treatment-related skeletal variants detected that were outside of the historical control range.

Examination of the incidence of spontaneous major malformations in the New Zealand White Rabbit was 55 cases out of 8036 fetuses examined by [redacted]. The incidence of spina bifida at this facility was 1 out of 8036 fetuses examined (0.01%).

Prenatal and postnatal development

Study title: Effects upon peri- and postnatal development in rats of Xylocaine given subcutaneously.

Key study findings: Female Sprague Dawley rats were treated with lidocaine (0, 2, 5 and 10 mg/kg, s.c.) from day 15 of pregnancy to weaning. The high dose of lidocaine (50 mg/kg) produced slight decreases in body weight and food consumption near the end of the treatment period. This dose may have decreased the maternal behavior as there was a slight decrease in the mean litter size and number of viable pups in this treatment group. Under the conditions tested, lidocaine did not significantly alter fertility or early embryonic development in the rat model.

Study no.:	79005 (Document No. T1756)
Volume #, and page #:	Volume 3 of 3, page 227
Conducting laboratory and location:	Astra Toxicology Laboratories Södertälje, Sweden
Date of study initiation:	January 15, 1979

Report Date March 12, 1986

GLP compliance: Not indicated

QA reports: yes (X) no ( )

Drug, lot #, and % purity: Lidocaine hydrochloride, batch 1073, 1066; purity _____ (Formulations also contained Metagin)

Methods

Doses: 0, 2, 10, 50 mg/kg

Species/strain: Sprague-Dawley Rats

Number/sex/group: 20 females/group

Route, formulation, volume, and infusion rate: Subcutaneous administration. Volume ranged from 0.2 to 2.5 ml/kg. Control animals received the vehicle, physiological saline at 2.5 mg/kg.

Satellite groups used for toxicokinetics: None.

Study design: Lidocaine was administered subcutaneously to pregnant rats once a day from day 15 of pregnancy to weaning (day 20 post parturition). The following table summarizes the study design:

Group	Number and sex	Animal reference number	Daily dose of µmol/kg	mg/kg	Administration volume, ml/kg
1	20 F	17/79 - 36/79	0	0	2.5
2	20 F	37/79 - 56/79	6.9	2	0.2
3	20 F	57/79 - 76/79	34.6	10	0.5
4	20 F	77/79 - 96/79	173.1	50	2.5

Parameters and endpoints evaluated: All dams were evaluated for mortality and clinical signs daily. Body weights were recorded on day 0 and then every 3rd day during gestation and on days 1, 7, 14 and 21 post parturition. Food consumption was determined weekly. Water consumption was determined weekly by visual inspection. Additional parameters examined included: duration of gestation period, nursing, lactation and parturition. Data collected from the F1 generation included the following: Litter size, number of living pups, gross abnormalities, sex, litter weight, pup weight. Physical development milestones were recorded, specifically pinna unfolding, tooth eruption and eye opening. Clinical signs in the F1 generation were monitored daily.

On day 21 post parturition all dams and litters were killed and all young were assessed for external and internal abnormalities. Microscopic evaluation of the thoracic and abdominal cavities of the dams was also completed.

Results

F_0 in-life: There were no moralities in the F_0 dams. The only clinical sign noted was a slight disturbance of the nursing was noted in the high dose dams which was described as

poor care taking of the pups. Body weights in the high dose group were slightly reduced (~6%) compared to controls during the lactation period. Food consumption was also slightly reduced in the high dose group (~19%) during the last few weeks of the study compared to controls. The length of the gestation period varied between 22 and 23 days for all groups. The sponsor's table below, however, suggests that the proportion of dams delivering on day 23 was increased in the high dose group compared to the control group. In the high dose group, the mean litter size was slightly reduced (8%) at birth and the number of viable pups was also reduced (26%) compared to controls. There was an apparent increase in pup loss due to increased neonatal mortality in the high dose group.

Group 1: Control (phys. saline) Group 3: Xylocain®, 34.6 µmol/kg

Group 2: Xylocain®, 6.9 µmol/kg Group 4: Xylocain®, 173.1 µmol/kg

Group	Number of rats with gestation period of (days)				
	22	23	24	25	Undetermined
1	15	3	0	0	0
2	18	0	0	0	0
3	14	2	1	0	0
4	9	7	1	0	0

F_0 necropsy: Data were not provided with the report nor discussed in the results section.

F_1 physical development: Lidocaine treatment did not increase the type or frequency of any gross malformations. The abnormalities noted are summarized by the sponsor's table below:

Incidence and types of abnormalities

Group 1:	Dam 31/79	One male pup showed atrophy of the left testis
Control	Dam 33/79	One female pup showed anophthalmia
	Dam 35/79	One male pup showed irregularities of the incisors in upper jaw
	Dam 36/79	Two female pups with aplasia of the tail were found at birth, both pups died later
Group 2:	Dam 39/79	One female and one male pup were slightly edematous at birth
Xylocain® 6.9 µmol/kg	Dam 50/79	One female pup showed anophthalmia
	Dam 55/79	One female pup with aplasia of the tail
	Dam 56/79	One female pup with aplasia of the tail
Group 3:	Dam 59/79	One male pup showed one small testis
Xylocain®	Dam 63/79	Two male pups with enlarged hearts
34.6 µmol/kg	Dam 67/79	One female pup with aplasia of the tail, died later
Group 4:	Dam 84/79	One female pup with aplasia of the tail
Xylocain®	Dam 92/79	One pup with aplasia of the tail
173.1 µmol/kg		

F_1 behavioral evaluation: There were no differences detected between treatment groups for the behavioral milestones examined.

F_1 reproduction: The reproductive capacity of the F_1 generation was not evaluated.

F_2 findings: The F_2 generation was not evaluated.

Study title: Effects upon Pregnancy and offspring development in rats of Lidocaine given intramuscularly with special reference to behavioral effects

Key study findings: Pregnant rats were treated with lidocaine (6 mg/kg, i.m., bilaterally into the masseter muscle) on day 10 and 11 of pregnancy. F1 pups were evaluated for lidocaine-induced alterations in post-natal development via behavioral and cognitive tasks. The results indicated that under the conditions of the assay, lidocaine treatment of pregnant rats during day 10 and 11 of pregnancy did not produce post-natal toxicity.

Study no.: 85035 (Document No. T1781)
Volume #, and page #: Volume 3 of 3, page 265
Conducting laboratory and location: Astra Toxicology Laboratories
Södertälje, Sweden

Date of study initiation: Report Date June 10, 1986
GLP compliance:
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Lidocaine hydrochloride, Batch 105, ~~~~ purity.

Methods

Doses: 6 mg/kg lidocaine was administered bilaterally into the masseter muscle of a group of 12 pregnant rats. Injections were administered once a day on days 10 and 11 of pregnancy. The rats were allowed to litter and the litters were normalized to 4 pups of each sex on day 3.

Species/strain: Sprague-Dawley Rat

Number/sex/group: 12 females/group

Route, formulation, volume, and infusion rate: Intramuscular injection, bilaterally. The control group received saline injections. Test article was dissolved in saline to produce a concentration of 7.5 mg/ml.

Satellite groups used for toxicokinetics:

Study design: The following table depicts the F_0 groups for the initial dosing. Offspring from the animals depicted in the table below constitute the F_1 generation. At weaning (day 25), 10 litters from each group were selected for further study. Behavioral testing in the F_1 animals was performed when offspring were between 60 and 80 days old.

Group	Number of animals	Animal reference number	Dose of lidocaine µmol/kg	mg/kg
1	12	1183/85-1194/85	-	-
2	12	1195/85-1206/85	21	6

Parameters and endpoints evaluated: Parameters tested in these studies included observation of clinical signs, individual body weight measurements (day 0 then every third day during gestation and on days 1, 3, 7, 14 and 21 post parturition. Food composition was determined weekly. Water consumption was assessed daily by visual inspection.

Clinical signs were evaluated during pregnancy, delivery and lactation. Clinical observations of the litters included litter size, mortality and abnormalities. Litter weights and the number of pups in each litter were recorded at delivery and again on day 7 and 21 post parturition. When necessary, fostering within the same group was used.

Physical development milestones included pinna unfolding, tooth eruptions and eye opening. Clinical signs of toxic effects on the offspring were recorded daily.

Developmental studies in the offspring included negative geotaxis testing on 5 consecutive days, from day 6. Locomotor activity, rearing behavior and total activity were measured over a 30-minute period. Groups for the behavioral testing included male and female control and lidocaine groups tested at 60 days and male control and lidocaine rats tested at 90 days of age.

Subgroups of F_1 animals were created consisting of 1 male and 1 female from each litter. The subgroups were selected for activity measurements. Subgroup 1 was used for activity measurements and tests of nociception (footshock, hot plate (58C) and tail flick (radiant heat), subgroup 2 was used for conditioned avoidance responding (CAR), subgroup 3 was used for light/dark discrimination tests and discrete reinforcement of low rates of responding and subgroup 4 was kept in reserve.

Swim maze test was completed at 25C. Two endpoints were monitored: Latency to reach and climb onto a platform and the number of trials which the animal failed to reach the platform during a 65-second swimming period.

Results

F_0 in-life: There were no mortalities or clinical signs noted in any treatment group. There were no differences in body weight gain, food consumption water consumption or length of gestation in the F_0 dams.

F_0 necropsy: No observations noted.

F_1 physical development: There were no differences in litter size or pup loss noted. There were no differences in mean pup weights at birth, day 7 or day 21 post parturition. All pups in both groups showed unfolded pinnas on day 4 and opened eyes on day 17. The tooth eruption occurred on days 11 and 12 in all pups.

F_1 behavioral evaluation: Lidocaine treatment did not alter the latency to geotaxis compared to control groups. There were no statistically significant differences in locomotor activity between groups. However, lidocaine treated males were slightly more active than controls and lidocaine treated females were slightly less active than controls. Likewise, lidocaine treated males showed slightly more rearing activity than controls, while lidocaine treated females showed slightly less rearing behavior than controls. A similar pattern was noted for motility between lidocaine males and females. There were no statistically significant differences between groups. Both groups reached a good level of responding with females slightly better than the males. Perinatal lidocaine exposure did not alter any tests of nociception. Lidocaine treated males were slightly better in light/dark discrimination than controls. Males in the control group showed significantly higher rate of responding to discrete reinforcement of low rates of responding than males in the lidocaine. In females there were no significant differences between groups, although there was a trend where the lidocaine rats received more reinforcement. There were no differences between lidocaine and control groups on performance in the swim maze test.

F_1 reproduction: Not examined.

F_2 findings: Not examined.

Study title: Reproduction study of citanest and xylocaine

Key study findings: The effects of lidocaine and prilocaine on reproduction in the rat model was examined following an 8 month daily treatment regimen with three separate mating periods between the F_0 animals. The key findings were as follows:

1. Treatment of both male and female rats daily over the course of 8 months with either 10 or 30 mg/kg lidocaine or prilocaine via subcutaneous injection resulted in little evidence for altered post-natal development in the offspring.
2. Both drug treatments significantly reduced the average number of pups per litter surviving until weaning in all three litters.
3. Both drugs at the high dose significantly reduced the average number of pups per litter at birth in the third litter only.

Study no.:	Document No. E16
Volume #, and page #:	Volume 3 of 3, page 265
Conducting laboratory and location:	Research Laboratories, AB Astra Södertälje, Sweden
Date of study initiation:	Report Date October 20, 1964
GLP compliance:	Not specified.
QA reports:	yes ( ) no (X)
Drug, lot #, and % purity:	Prilocaine and lidocaine batch numbers and purity records not included in the submission.

Methods: This is a reproductive toxicology study that treats the animals daily throughout the course of three different mating periods and examines the effects on the offspring. Animals were injected via the subcutaneous route of administration with saline control, prilocaine or lidocaine. Eight successive injection sites were rotated to minimize local irritation. Animals were weighed weekly and doses corrected for change in body weight. The treatment period extended over eight months, during which time, the animals were mated three times. The first mating occurred after 2 months of treatment. The litter which resulted from the first mating were counted and weighed at birth, returned to the mother until weaning (day 21). At weaning, the pups were weighed, examined carefully, sexed and discarded. The parents were remated after randomizing within the respective group 14 days after weaning the first group. The resulting litters were counted, weighed, returned to mothers until weaning. At weaning age, pups were weighed, examined, sexed and discarded. One third of the pups of group I, III and V were autopsied and one-third were killed with chloroform and X-rayed for signs of skeletal abnormalities. All other animals were discarded. A third litter was obtained and evaluated in a similar fashion.

Doses: 0, 10 and 30 mg of either prilocaine or lidocaine

Species/strain: Sprague Dawley rat

Number/sex/group: 30/sex/group

Route, formulation, volume, and infusion rate: Subcutaneous injection of drug in a saline solution, volume of 3 ml/kg in control animals.

Satellite groups used for toxicokinetics: Not completed.

Study design: The table below summarizes the group tested:

Group #	Dose
Group I	0
Group II	10 mg Citanest
Group III	30 mg Citanest
Group IV	10 mg Xylocaine
Group V	30 mg Xylocaine

Parameters and endpoints evaluated: Animals that died or were killed during the trial were autopsied. Pups that survived to weaning were examined for external evidence of malformations. Pups that died prior to weaning, those dying in the post-natal period were fixed *in toto* in formalin and examined for external visible malformations. The larger pups were autopsied and histological assessment of the heart, liver, kidneys, spleen and bone marrow was completed, if available. One third of the pups from the second mating of groups I, III and V were killed at weaning and autopsied. Another third of the pups were killed and examined for skeletal abnormalities via X-rays (bodies frozen for future reference).

Results

F_0 in-life: No observations recorded.

F_0 necropsy: No observations recorded.

F_1 physical development: Treatment of the F0 animals with lidocaine or prilocaine did not alter the number of litters produced, the average number of pups born per litter, the average weight of pups at birth and at weaning or the distribution of sex among pups. The high dose of lidocaine and prilocaine produced a significant decrease in the average number of pups per litter at birth in the third litter only. Treatment with lidocaine or prilocaine did produce a significant decrease in the average number of pups per litter surviving until weaning age. There were no obvious treatment-related malformations noted in any of the pups examined in the first, second or third litters under the conditions of this study.

Average number of pups per litter at birth					
Group	Group 1	Group 2	Group3	Group 4	Group 5
Treatment	**Saline**	**Lidocaine 10**	**Lidocaine 30**	**Prilocaine 10**	**Prilocaine 30**
Litter 1	12.8 ± 0.8	12.6 ± 0.6	13.3 ± 0.4	12.6 ± 0.6	12.2 ± 0.7
Litter 2	14.4 ± 0.4	13.7 ± 0.5	13.7 ± 0.6	13.5 ± 0.4	12.9 ± 0.7
Litter 3	14.2 ± 0.6	13.2 ± 0.4	11.9 ± 0.7*	12.6 ± 0.7	12.3 ± 0.5*

Average number of pups per litter surviving until weaning age					
Group	**Group 1**	**Group 2**	**Group3**	**Group 4**	**Group 5**
Treatment	**Saline**	**Lidocaine 10**	**Lidocaine 30**	**Prilocaine 10**	**Prilocaine 30**
Litter 1	81%	53%*	51%*	69%*	54%*
Litter 2	83%	61%*	61%*	68%*	78%*
Litter 3	86%	92%	82%*	87%	91%

* $p < 0.05$ compared to group 1 control animals

F_1 behavioral evaluation: Not completed.

F_1 reproduction: Not completed.

F_2 findings: Not completed.

3.4.7 Local tolerance

There were no additional local tolerance studies submitted for this cycle of the NDA review.

3.4.8 Special toxicology studies

There were no special toxicology studies submitted for this cycle of the NDA review.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The sponsor has provided additional data to characterize the genetic toxicology and reproductive toxicology endpoints associated with drug products that has been lacking from the label for both of these drugs. The studies, although perhaps not up to current standards; provide an adequate characterization of these two drugs which have been on the market for many years. The vast clinical experience provides additional confidence in the safety of the drug product. Based upon the review of the data, the drug product appears to be reasonable safe and the potential for toxicity appears to be low for the given indication.

Unresolved toxicology issues (if any): The effect of prilocaine on perinatal and postnatal development has not been fully characterized. The behavioral observations on the F1 generation and fertility were not tested. These parameters will be examined in the Segment III study on prilocaine that will be completed as a phase 4 commitment.

Recommendations: Based upon review of the additional information submitted for this review cycle, the sponsor has addressed the concerns of the Division regarding adequate characterization of the potential for genetic and reproductive toxicity of lidocaine and prilocaine. From the pharmacology/toxicology perspective, the NDA is approvable.

Following labeling negotiations on December 19, 2003, the sponsor agreed to the following phase IV commitment:

> We commit to completing a Segment III Reproductive Toxicology study on prilocaine in a single species as described ICH-S5A Guidance to Industry. The adverse effects to be assessed will include measurements of altered growth and development and functional deficits in the offspring, including behavior, maturation (puberty) and reproduction (F1). Sensory functions, reflexes and behavioral responses will be assessed in the F1 generation. We commit to finalizing the study protocol by May of 2004, start dosing by July of 2004 and submit the final study report by July of 2005.

Suggested labeling: The agreed upon labeling for the non-clinical sections of the Oraqix label are reproduced below with the sponsor's final adjustments. These comments were discussed during the December 19, 2003 telecon.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

Carcinogenesis - Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or prilocaine. Chronic oral toxicity studies of o-toluidine, a metabolite of prilocaine, have shown that this compound is a carcinogen in both mice and rats. The tumors associated with o-toluidine included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/ adenomas in female rats. These findings were observed at the lowest tested dose of 150 mg/kg/day or greater over two years (estimated daily exposures in mice and rats were approximately 6 and 12 times, respectively, the estimated exposure to o-toluidine at the maximum recommended human dose of 8.5 g of Oraqix gel on a mg/m^2 basis). Thus, the no effect dose is less than 6 to 12 times the estimated exposure to o-toluidine at the maximum recommended human dose, assuming 100% bioavailialbility of prilocaine from the Oraqix gel. Complete conversion of prilocaine to its metabolite o-toluidine on a molar basis is assumed. This gives a conversion on a weight

basis of about 50% for prilocaine base (dependent on the molecular weights, i.e. 220 for prilocaine base and 107 for o-toluidine).

Mutagenesis - The mutagenic potentials of lidocaine and prilocaine have been tested in the Ames Salmonella reverse mutation assay, an in vitro chromosome aberrations assay in human lymphocytes and in an in vivo mouse micronucleus assay. There was no indication of any mutagenic effects for either compound in these studies.

o-Toluidine, a metabolite of prilocaine, was positive in Escherichia coli DNA repair and phage-induction assays. Urine concentrates from rats treated orally with 300 mg/kg o-toluidine were mutagenic to Salmonella typhimurium in the presence of metabolic activation. Several other tests on o-toluidine, including reverse mutations in five different Salmonella typhimurium strains with or without metabolic activation, and single strand breaks in DNA of V79 Chinese hamster cells, were negative.

IMPAIRMENT OF FERTILITY: The effect of lidocaine on fertility was examined in the rat model. Administration of 30 mg/kg, s.c. (180 mg/m^2 or 1.4 fold the maximum recommended human oral dose for one treatment session assuming 100% bioavailability of lidocaine) to the mating pair did not produce alterations in fertility or general reproductive performance of rats. There are no studies that examine the effect of lidocaine or prilocaine on sperm parameters. The effects of prilocaine on fertility was examined in rats treated for 8 months with 10 or 30 mg/kg, s.c. lidocaine or prilocaine (60 mg/m^2 and 180 mg/m^2 on a body surface area basis, respectively up to 1.4-fold the maximum recommended exposure for a single procedure assuming 100% bioavailability of lidocaine and prilocaine). This time period encompassed 3 mating periods. There was no evidence of altered fertility.

USE IN PREGNANCY:

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats with lidocaine, prilocaine and a 1:1 (weight:weight) mixture of the two compounds. There was no evidence of harm to the fetus at subcutaneous doses of up to 30 mg/kg lidocaine (estimated exposure was approximately equivalent to the expected lidocaine exposure at the maximum recommended human dose of Oraqix gel on a mg/m^2 basis). Following intramuscular prilocaine doses of up to 300 mg/kg (estimated exposure was approximately 11 times the expected prilocaine exposure at the maximum recommended human dose of Oraqix gel on a mg/m^2 basis), there was no evidence of impaired fertility or harm to the fetus. Similarly, subcutaneous administration of a lidocaine and prilocaine mixture of 40 mg/kg of each compound (estimated exposures were approximately 1.5 times the expected lidocaine and prilocaine exposures at the maximum recommended human dose of Oraqix gel on a mg/m^2 basis) produced no teratogenic, embryotoxic, or fetotoxic effects. Reproductive toxicology studies of lidocaine were also conducted in rabbits. There was no evidence of harm to the fetus at a dose of 5 mg/kg, s.c. (60 mg/m^2). Treatment of rabbits with 15 mg/kg (180 mg/m^2) produced evidence of maternal toxicity and evidence of delayed fetal development, including a non-significant decrease in fetal weight (7%) and an increase in minor skeletal anomalies (skull and sternebral defects, reduced ossification of the phalanges). The effects of lidocaine and prilocaine on post-natal development was examined in rats treated for 8 months with 10 or 30 mg/kg, s.c. lidocaine or prilocaine (60 mg/m^2 and 180 mg/m^2 on a body surface area basis, respectively up to 1.4-fold the maximum recommended exposure for a single procedure). This time period encompassed 3 mating periods. There was no evidence of altered post-natal development in any offspring, however, both doses of either drug significantly reduced the average number of pups per litter surviving until weaning of offspring from the first 2 mating periods. All the above calculations of exposure are assuming 100% bioavailability of lidocaine and prilocaine after Oraqix administration. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Oraqix should be used during pregnancy only if the benefits outweigh the risks.

Reproduction studies on the Oraqix drug product, including the inactive ingredients, have not been conducted.

Signatures (optional):

Reviewer Signature R. Daniel Mellon, Ph.D.

Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No

3.7. APPENDIX/ATTACHMENTS

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/s/

R. Daniel Mellon
12/19/03 08:57:59 PM
PHARMACOLOGIST

NDA 21-451: Oraqix Periodontal Gel
Addendum to the Original NDA review
Author: Timothy J. McGovern, Ph.D., Supervisory Pharmacologist
Date: November 20, 2002

This addendum pertains to the "Recommendation for Nonclinical Studies:" of the original NDA review under the Executive Summary (dated November 18, 2002). The first recommendation states that "an in vitro and an in vitro chromosome aberration study." should be performed to fully characterize the genotoxic potential of prilocaine.

The comment should read as follows:

The following genetic toxicology studies should be performed in order to fully characterize the genotoxic potential of prilocaine: an in vitro and an in vivo chromosome aberration study chromosome aberration study. These studies may be completed as a Phase 4 commitment. The sponsor should provide commitments for the timing of submission of study protocols, initiation of studies and submission of final study reports.

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/s/

Timothy McGovern
11/20/02 11:09:19 AM
PHARMACOLOGIST

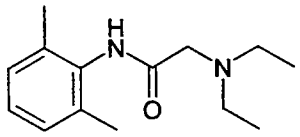
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-451
Review number: 1
Sequence number: 000 /January 23, 2002/Original Application
Information to sponsor: Yes (X) No ( )
Sponsor: DENTSPLY Pharmaceuticals, York, PA
Manufacturer for drug substance: AstraZeneca, AB, Bjorkborn, Sweden

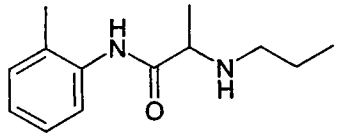
Reviewer name: Timothy J. McGovern, Ph.D.
Division name: Anesthetics, Critical Care, and Addiction Drug Products
HFD #: 170
Review completion date: November 18, 2002

Drug:

Trade names: Oraqix Peiodontal Gel
Generic name: lidocaine; prilocaine
Code name: None
Chemical names:
Lidocaine: 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide
Prilocaine: N-(2-methyl-phenyl)-2-(propylamino)-propanamide
CAS registry number:
Lidocaine: 137-58-6
Prilocaine: 721-50-6
Mole file number: None
Molecular formula/molecular weight:
Lidocaine: $C_{14}H_{22}N_2O$/234.3
Prilocaine: $C_{13}H_{20}N_2O$/220.3
Structure:
Lidocaine:



Prilocaine:



Relevant INDs/NDAs/DMFs: IND 52,677 (Oraqix); NDA 19-941 (EMLA Cream)

Drug class: amide class of local anesthetics

Indication: Localized anesthesia in periodontal pockets for scaling and/or root planing

Clinical formulation:

Ingredient	Quantity (mg)	Function
Lidocaine	25	
Prilocaine	25	
Poloxamer 188 purified		
Poloxamer 407 purified		
Hydrochloric acid, Ph. Eur., NF		
Water purified, Ph. Eur., USP		

Route of administration: Oral (dental gel for oral mucosa)

Proposed use: On average, one cartridge (1.7 g) or less will be sufficient for one quadrant of the dentition. The maximum recommended dose of Oraqix at one treatment session is 5 cartridges (8.5 g gel containing 212.5 mg lidocaine base and 212.5 mg prilocaine base). Periodontal pockets should be filled with Oraqix until the gel becomes visible at the gingival margin. The duration of anesthesia is about 20 minutes. If anesthesia starts to wear off, Oraqix is reapplied as needed.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-451 is approvable from a nonclinical perspective.

B. Recommendation for Nonclinical Studies

1. The following genetic toxicology studies should be performed in order to fully characterize the genotoxic potential of prilocaine: an in vitro and an in vitro chromosome aberration study. These studies may be completed as a Phase 4 commitment. The sponsor should provide commitments for the timing of submission of study protocols, initiation of studies and submission of final study reports.

2. The following reproductive toxicology studies should be performed to fully characterize the reproductive effects of lidocaine and/or prilocaine: A fertility study with lidocaine, embryo-fetal development studies in rabbits with lidocaine and prilocaine, and a pre- and post-embryo-fetal development study with lidocaine. These studies may be completed as a Phase 4 commitment. The sponsor should provide commitments for the timing of submission of study protocols, initiation of studies and submission of final study reports.

C. Recommendations on Labeling

A label review was performed and is detailed under Section X. The "Mutagenesis", "Fertility" and "Pregnancy" sections should be updated once the requested studies are performed and reviewed. Animal-to-human exposure ratios differ from those proposed by the sponsor primarily due to differences in the assumed magnitude of drug absorption used for the calculations. Although the sponsor's calculations assumed 40% drug absorption of the drug components for the human use of Oragix gel, Dr. David Lee, the Biopharmaceutics reviewer for this NDA, indicated that the information submitted to support this claim did not adequately do so. Thus, the exposure ratios were calculated with a conservative assumption of 100% absorption.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

The only new studies performed for this application were two acute toxicology studies in rats with lidocaine and prilocaine at maximally tolerated doses using the oral route of administration. These studies produced no unexpected toxicities; findings were primarily related to CNS effects and were typical of high-dose effects of local anesthetics. Exposures to both the parent compounds and their major metabolites, 2,6-xylidine and o-toluidine, were observed. The observed plasma levels were greater than that expected following the maximum proposed use of Oraqix gel. A local irritation study with an initial formulation containing unpurified poloxamers was performed in dogs and produced no signs of irritation following repeated

administration to the gingival sulcus. Information provided by the sponsor to support the safety of the proposed use of purified poloxamers 188 and 407 is considered adequate.

Genetic toxicity tests with lidocaine and prilocaine produced negative results although a complete battery of studies was not performed with prilocaine. Similarly, reproductive studies with lidocaine and prilocaine produced no effects although a complete battery of studies was not performed.

B. Pharmacologic Activity

Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Local anesthetics can also bind to other membrane proteins such as K^+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K^+ channels since the interaction of local anesthetics with K^+ channels requires higher drug concentrations. Lidocaine and prilocaine have similar pharmacological profiles and are about equipotent. Lidocaine is considered to be the faster acting of the two components, although are more short-acting in comparison to bupivacaine. Prilocaine causes little vasodilation and can be used without a vasoconstrictor and its increased volume of distribution reduces its CNS toxicity.

Pharmacology studies performed under NDA 19-941 showed that eutectic mixtures of lidocaine and prilocaine over the range of 0.55 to 10% (total anesthetic base) produced a concentration-related analgesia upon a 60-minute contact with both unabraded and abraded skin in guinea pigs. Almost no block was observed with a 0.55% emulsion, whereas an 80% block of normal responses to pin pricking was observed with 2.5 to 10% emulsions. Analgesia lasted approximately 60 minutes or greater. The analgesia of the combination was more profound and lasted longer than that produced by an equivalent amount of either lidocaine or prilocaine given alone. The formulations were more effective on abraded skin than on intact skin.

C. Nonclinical Safety Issues Relevant to Clinical Use

None at this time.

III. Administrative

A. **Reviewer signature:** _____
Timothy J. McGovern, Ph.D.

B. **Supervisor signature:** **Concurrence -** _____
Timothy J. McGovern, Ph.D.

C. **cc: list:**

Introduction and Drug History: Lidocaine 2.5% and Prilocaine 2.5% Periodontal Gel is an extension of the development program for EMLA Cream (NDA 19-941), a topical anesthetic approved for use on normal skin, male genital skin and female genital mucosa membrane. Like EMLA Cream, the Periodontal Gel derives its anesthetic activity from a eutectic mixture of lidocaine and prilocaine in a 1:1 ratio. The Periodontal Gel, however, is designed to function on the oral mucosa. Whereas EMLA cream will not stay within periodontal pockets due to a reduction in viscosity, Oraqix is formulated with gelling agents such that the product is fluid at room temperature. However, when introduced into a periodontal pocket, the gel remains in the periodontal pocket in a state of increased viscosity for the time necessary to introduce local anesthesia.

IND 52,677 (lidocaine/prilocaine dental gel) was opened in 1997 by Astra USA to evaluate the anesthetic efficacy and safety of the dental gel with a maximum dose of 7.2 grams. This product was eventually sold to DENTSPLY.

A letter dated August 25, 2000, was sent to the sponsor Inc.) informing them that since the new poloxamer components no longer meet NF and have not undergone safety testing in animals, chemical and toxicological characterization of the new poloxamer agents would be needed before the NDA submission. A bridging toxicology study may be required before Phase 3 clinical trials if the components are found to differ chemically from the original gelling agents. Secondly, the sponsor was asked to provide the final ortho-toluidine content in the final drug product for clinical use. Due to the carcinogenic risk of o-toluidine to humans, the amount present in the final drug product should be limited to the lowest feasible concentration or no greater than the permitted exposure level (PEL) or Threshold Limit Value (TLV) for Chemical Substances and Physical Agents Biological Exposure Indices). Also, the product label should include a discussion of the carcinogenic risk of o-toluidine, and monitoring of plasma levels should continue in the clinical studies.

In a Pre-NDA meeting held on April 24, 2001 with AstraZeneca, R&D, and Dentsply, Inc., the sponsors were informed that a more detailed description of the purification process as well as an executed batch record would be needed before the Agency agrees that adequate support is provided for an NDA. Additionally, the preclinical information in the meeting package support the submission of an NDA and, given sufficient clinical and nonclinical experience with the proposed formulation including lidocaine, prilocaine, metabolites and poloxamers, a bridging study would not be required, pending review by the CMC group. The sponsors were informed that there is no reason to believe that the purified poloxamers will be more toxic than the originally non-toxic, non-purified poloxamers. The sponsors were asked to provide Letter of Authorization to reference DMFs for the poloxamers and literature references on the potential poloxamer toxicity. It was stated that the premise for not requesting a bridging study is that there is no evidence of risk of the unpurified poloxamer. If adequate documentation of safety is not provided, the Agency will need a bridging study. The sponsor was encouraged to provide assurances for the application that the poloxamers have no toxicity before submitting it to the Agency and that resolution of this issue was encouraged prior to submission of the NDA.

Studies reviewed in this NDA submission:

Studies	Doc. #	Volume
General Toxicology:		
Lidocaine hydrochloride monohydrate (AR-P111001UZ): Single oral (gavage) MTD study in rats	SR00609-01	8
Prilocaine hydrochloride (AR-P111002AA): Single oral (gavage) MTD study in rats	SR01048-01	8
Genotoxicity:		
Mutagenicity evaluation of prilocaine in the Ames Salmonella/Mammalian microsome mutagenicity test	T1929	7
Mouse micronucleus test of lidocaine	T1968	7

Studies previously reviewed:

	Doc. #	Volume	Review / date
Pharmacology:			
Percutaneous local anesthesia in the guinea pig by emulsions of an eutectic mixture of Citanest and Xylocaine	802-10 A 135-02	5	N19941, 1/89
Topical local anesthetic effect of an eutectic mixture of Citanest and Xylocaine on abraded skin in the guinea pig	802-10 A 137-02	5	N19941, 1/89
Pharmacokinetics and Toxicokinetics:			
Evaluation of plasma concentrations of lidocaine and prilocaine in the study: General toxicity of EMLA given rectally to dogs for one month	802-10 AF 42-1	6	N19941, 11/99
Toxicology:			
Acute toxicity of Xylocaine and Citanest (1:1) in male mice after IV injection	T1349	6	N19941, 1/89
Acute toxicity of Xylocaine and Citanest (1:1) in male rats after IV injection	T1330	6	N19941, 1/89
Acute toxicity of lidocaine, prilocaine and EMLA in male rats after SC injection	T1372	6	N19941, 1/89
Acute toxicity of EMLA cream in rabbits after single dermal administration	T1373	6	N19941, 1/89
General toxicity of EMLA given rectally to dogs for one month	T1608	6	N19941, 11/99
Genotoxicity:			
Mutagenicity evaluation of LEA152 in the Ames Salmonella/Mammalian microsome mutagenicity test	T2355	7	N19941, 6/92
Analysis of structural chromosome aberrations in human lymphocytes treated with lidocaine HCl monohydrate (LEA152) in vitro	T2376	7	N19941, 6/92
Mouse micronucleus test of lidocaine HCl monohydrate	T2362	7	N19941, 6/92
Mutagenicity evaluation of 2,6-xylidine in the L5178Y mouse lymphoma cell thymidine kinase locus mutagenicity test	T2183	6	?
Reproductive Toxicology:			
Effects on pregnancy in rats of a lidocaine:prilocaine (1:1) mixture given SC – a DRF study	T2412	7	N19941, 6/92
Effects on pregnancy in rats of a lidocaine:prilocaine (1:1) mixture given SC	T2413	7	N19941, 6/92

Special Toxicology:			
Vaginal irritation, in dogs, after topical administration of Xylocaine/Citanest (EMLA) on 20 consecutive days	T1163	7	N19941, 1/89 N19941, 11/99
Irritation of intact skin, in rabbits, after 24 hours occlusive epicutaneous administration of Xylocaine/Citanest emulsion	T1017	7	N19941, 1/89
Skin irritation, in the rabbit, after epicutaneous application of Xylocaine/Citanest (EBLA) for 1 hr a day on 20 consecutive days	T1128	7	N19941, 1/89
Eye irritation in rabbits after single administration of Xylocaine/Citanest emulsion	T1018	7	N19941, 1/89

Studies Not Reviewed in this NDA: None

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology summary: No new pharmacology studies were performed by the sponsor for this application. A review of the pharmacology of local anesthetics in general, and lidocaine and prilocaine specifically, is provided in Goodman and Gilman's The Pharmacological Basis of Therapeutics. When applied locally to nerve tissue in appropriate concentrations, local anesthetics reversibly block the action potentials responsible for nerve conduction. A local anesthetic in contact with a nerve trunk can cause both sensory and motor paralysis in the area innervated. The action is reversible at clinically relevant concentrations; complete recovery in nerve function occurs with no evidence of damage to nerve cell fibers or cells.

Local anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Local anesthetics can also bind to other membrane proteins such as K^+ channels. However, blockade of conduction is not accompanied by any large or consistent change in resting membrane potential due to block of K^+ channels since the interaction of local anesthetics with K^+ channels requires higher drug concentrations. Lidocaine and prilocaine have similar pharmacological profiles and are about equipotent. Lidocaine is considered to be the faster acting of the two components, although are more short-acting in comparison to bupivacaine. Prilocaine causes little vasodilation and can be used without a vasoconstrictor and its increased volume of distribution reduces its CNS toxicity.

No nonclinical pharmacology studies using a relevant animal model were performed with the current proposed formulation. Pharmacology studies in guinea pigs performed under NDA 19-941 showed that eutectic mixtures of lidocaine and prilocaine over the range of 0.55 to 10% (total anesthetic base) produced a concentration-related analgesia upon a 60-minute contact with both unabraded and abraded skin. Almost no block was observed with a 0.55% emulsion, whereas an 80% block of normal responses to pin pricking was observed with 2.5 to 10% emulsions. Analgesia lasted approximately 60 minutes or greater. The analgesia of the combination was more profound and lasted longer than that produced by an equivalent amount of either lidocaine or prilocaine given alone. The formulations were more effective on abraded skin than on intact skin.

Pharmacology conclusions: The pharmacology of the local anesthetics lidocaine and prilocaine is well known. The anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Lidocaine and prilocaine have similar pharmacological profiles although some differences are noted. Although the sponsor performed no pharmacology studies with the current formulation, studies performed with the drug combination at similar concentrations in a cream or emulsion under NDA 19-941 produced concentration-related analgesia upon a 60-minute contact with both unabraded and abraded skin.

II. SAFETY PHARMACOLOGY:

Safety Pharmacology Summary: Formal safety pharmacology studies were not performed for this application and were not required due to the extensive human experience with both lidocaine and prilocaine. As with other local anesthetics, secondary pharmacodynamic effects of lidocaine and prilocaine include stimulation of the CNS as illustrated by restlessness and tremor leading to clonic convulsions. Central stimulation is followed by depression and death is usually caused by respiratory failure. Cardiovascular system effects may include decreased electrical excitability, conduction rate, force of contraction, arteriolar dilatation, and cardiac arrythmias when plasma levels exceed ~ 10 µmol/L (5 mg/L) for either compound. Cardiovascular effects are thought to be due to a pharmacological effect on sodium channel blockade. These findings were confirmed in acute toxicology studies performed under NDA 19-941 in which reduced motor activity, unconsciousness, respiratory distress, twitching and/or cyanosis were observed in mice and rats for up to one hour following IV administration of a 1:1 mixture. Similar findings were noted in rats following subcutaneous administration. Lidocaine has a biphasic effect on blood flow. Lower concentrations are vasoconstrictive, while higher concentrations are vasodilataing.

Safety Pharmacology Conclusions: The primary effects of lidocaine and prilocaine related to safety pharmacology include CNS and cardiovascular effects at plasma levels exceeding ~ 10 µmol/L (5 mg/L) for either compound. Plasma levels following administration of Oraqix Periodontal Gel are expected to be well below the plasma levels at which these adverse findings are observed.

III. PHARMACOKINETICS AND TOXICOKINETICS

No new pharmacokinetic or toxicokinetic studies were performed for this application. The sponsor referred to studies performed previously under NDA 19-941 or information in the published literature.

PK/TK Summary: Lidocaine and prilocaine bases are absorbed rapidly through mucous membranes, intact and damaged skin, and from the intestines and respiratory tract. The hydrochlorides are absorbed rapidly after parenteral administration, but absorption through intact skin or mucous membranes is poor. Lidocaine and prilocaine are widely distributed into highly perfused tissue, followed by redistribution into skeletal muscle and adipose tissue. Distribution is similar for both compounds although the volume of distribution is greater for prilocaine. Lidocaine affinity for melanin has been demonstrated using labeled compound resulting in a longer elimination half-life in pigmented skin. Lidocaine readily crosses the placenta and blood brain barrier with plasma levels declining in parallel that of the mother animal. Lidocaine protein binding is approximately 66% in humans and 78% in dogs. Protein binding of prilocaine in humans is approximately 30%; no information in animals is available.

Lidocaine is almost completely metabolized before excretion with the liver as the primary site. Metabolism is qualitatively similar across species with quantitative variations. The three main types of metabolic reactions include aromatic hydroxylation, N-dealkylation and amide

hydrolysis, followed by conjugation reactions. Major enzymes involved in lidocaine metabolism in human liver microsomes were CYP3A4 and CYP1A2. In a human liver slice system, MEGX and 2,6-xylidine were identified as major metabolites. In the urine of man and dogs, the major metabolite (4-hydroxy 2,6-xylidine) accounted for 70% and 35% of the dose, respectively. In rats, the urinary metabolites accounted for 70% of the administered dose and included 3-hydroxy lidocaine and its dealkylated product, 3-hydroxy-MEGX. Prilocaine is rapidly and extensively metabolized to o-toluidine and its hydroxylated derivatives, as well as to N-propylalanine, in both animals and man. Most of the metabolites are excreted as conjugated as either sulphates, glucuronides, or are acetylated; enzymes involved are not known.

Plasma concentrations of lidocaine generally rapidly decline after an IV dose, with an initial half-life of 30 minutes. The elimination half-life is generally 1-2 hours. There is a large variability in clearance among species with humans demonstrating a clearance of 13 ml/min kg up to 130 ml/min kg in rats. Excretion of lidocaine in breast milk has been demonstrated in humans after use in dental surgery with milk:plasma ratios for lidocaine and MEGX of 1:1 and 1:8; excretion in breast milk has not been studied in animals. Prilocaine undergoes significant elimination by extrahepatic organs, differing from other local anesthetics. The elimination half-life is generally 1.3 hours in dogs and 2.2 hours in rabbits, similar to the 1.6 hour half-life reported in humans.

PK/TK Conclusions: Lidocaine and prilocaine bases are absorbed rapidly through mucous membranes, intact and damaged skin, and from the intestines and respiratory tract. The hydrochlorides are absorbed rapidly after parenteral administration, but absorption through intact skin or mucous membranes is poor. Both lidocaine and prilocaine are absorbed and extensively distributed and metabolized. The major metabolites include MEGX and 2,6-xylidine (lidocaine) and o-toluidine (prilocaine). Elimination half-lives across species for both compounds are in the range of 1-2 hours.

IV. GENERAL TOXICOLOGY:

The sponsor performed single dose oral (gavage) studies in rats with lidocaine and prilocaine to characterize the potential toxicity of these compounds at maximal oral doses. Studies using other routes of administration were performed under the development program for EMLA Cream and are summarized below.

Study Title: Lidocaine hydrochloride monohydrate (AR-P111001UZ): Single oral (gavage) MTD study in rats

Key Study Findings:

- The maximum non-lethal dose was 400 mg/kg in males and 200 mg/kg in females; the minimum lethal dose was 630 mg/kg in males and 400 mg/kg in females.
- Clinical observations are CNS related, occurred between 15 minutes and 5 hours after dosing, and are findings associated with high doses of local anesthetics.
- High systemic exposure was observed for both lidocaine and 2,6-xylidine. Although lidocaine exposure was higher in females at a lower dose of lidocaine compared to males, the relative amount of 2,6-xylidine was greater in males.

Study #: 00609
Volume # and page #: 8/Ref. 30
Conducting laboratory and location: Astra Zeneca R&D Sodertalje, Sweden
Date of study initiation: February 2001
GLP compliance statement: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel and % purity: lidocaine hydrochloride monohydrate, 300001-13, NA, [redacted]
Formulation/vehicle: dissolved in purified water

Methods: Sprague Dawley rats (2-5/sex/dose, 7-9 weeks old) were administered single oral doses of 520, 850, 1700 and 2700 mcmol/kg (120, 200, 400 and 630 mg/kg, 5 ml/kg). The lowest dose was only given to females and the highest dose was only given to males. A control group receiving tap water was included. Surviving animals were necropsied 3-5 days after dosing. Observations included clinical signs, body weight, gross pathology. Blood samples were taken in satellite animals at a dose level of 120 mg/kg in males and 80 mg/kg in females for determination of lidocaine and 2,6-xylidine plasma levels.

Results:

Mortality: The maximum non-lethal dose was 400 mg/kg in males and 200 mg/kg in females; the minimum lethal dose was 630 mg/kg in males and 400 mg/kg in females. The animals were killed in moribund condition within 15 minutes of dosing.

Mortality incidence.

Gender	Dose (mg/kg)					
0		80	120	200	400	630
Male	0/5	-	0/5	0/2	0/5	1/5
Female	0/5	0/5	0/2	0/2	1/5	-

-: no animals administered this dose

Clinical signs: Observed clinical signs considered to be drug-related are summarized below. The findings are primarily CNS related, occurred at all doses between 15 minutes and 5 hours after dosing, and are findings commonly associated with high doses of local anesthetics. Convulsions were observed at doses greater than 80 mg/kg in females and 400 mg/kg in males.

Clinical signs	Dose (mg/kg)									
	0		80	120		200		400		630
	M	F	F	M	F	M	F	M	F	M
Decreased motor activity	0/5	0/5	3/5	4/5	2/2	1/2	2/2	5/5	4/5	5/5
Ataxia	0/5	0/5	2/5	1/5	1/2	2/2	2/2	5/5	4/5	1/1
Half-shut eyes	0/5	0/5	1/5	0/5	2/2	0/2	1/2	2/5	3/5	4/5
Increased respiration depth	0/5	0/5	0/5	1/5	1/2	0/2	1/2	0/5	2/5	1/1
Piloerection	0/5	0/5	0/5	2/5	2/2	2/2	2/2	1/5	3/5	3/5
Tonic convulsions	0/5	0/5	0/5	0/5	1/2	0/2	0/2	0/5	1/1	0/5
Loss of righting reflex	0/5	0/5	0/5	0/5	0/2	0/2	1/2	0/5	3/5	2/5
Clonic convulsions	0/5	0/5	0/5	0/5	0/2	0/2	0/2	0/5	3/5	1/5
Hunched posture	0/5	0/5	0/5	0/5	0/2	0/2	0/2	0/5	2/5	0/5
Respiratory disturbance	0/5	0/5	0/5	0/5	0/2	0/2	0/2	0/5	0/5	0/5

Body weight: No drug-related changes in body weight gain were noted.

Gross pathology: No findings related to drug treatment were observed.

Toxicokinetics: High systemic exposure was observed for both lidocaine and 2,6-xylidine. Although lidocaine exposure was higher in females at a lower dose of lidocaine compared to males, the relative amount of 2,6-xylidine was greater in males.

Target dose (mg/kg)	Gender	Compound	Cmax, mean (mcmol/L) (range)	AUC (0-4h) (mcmol.hr/L)	Tmax (min)	t1/2 (hr)
120 mg/kg	M	Lidocaine 2,6-xylidine	6.6 (3.9-12) 3.3 (2.6-3.8)	6 7.9	15 60	2.4 2
80 mg/kg	F	Lidocaine 2,6-xylidine	25 (17-32) 0.97 (0.72-1.3)	17 2.2	15 60	2.3 3.4

Summary of individual study findings: The maximum non-lethal dose was 400 mg/kg in males and 200 mg/kg in females; the minimum lethal dose was 630 mg/kg in males and 400 mg/kg in females. Clinical observations are CNS related, occurred between 15 minutes and 5 hours after dosing, and are findings associated with high doses of local anesthetics. High systemic exposure was observed for both lidocaine and 2,6-xylidine. Although lidocaine exposure was higher in females at a lower dose of lidocaine compared to males, the relative amount of 2,6-xylidine was greater in males. Plasma levels at the lowest doses tested in males and females are ~ 4 and 15 times greater than the expected maximum total lidocaine and prilocaine plasma level (1.7

mcmol/L) following the proposed use of Oraqix gel.

Study Title: Prilocaine hydrochloride (AR-P111002AA): Single oral (gavage) MTD study in rats

Key Study Findings:

- The maximum non-lethal dose was 1300 mg/kg in males and 880 mg/kg in females; the minimum lethal dose was 1300 mg/kg in females and no deaths were observed in males.
- Clinical observations are CNS related, occurred between 15 minutes and 5 hours after dosing, and are findings associated with high doses of local anesthetics.
- Systemic exposure was observed for both prilocaine and o-toluidine. Kinetic data indicates that exposure is ~ 2-fold greater in females at comparable doses.

Study #: 01048
Volume # and page #: 8/Ref. 31
Conducting laboratory and location: Astra Zeneca R&D Sodertalje, Sweden
Date of study initiation: February, 2001
GLP compliance statement: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel and % purity: prilocaine hydrochloride, 300000-12, NA, ——
Formulation/vehicle: dissolved in purified water

Methods: Sprague Dawley rats (2-5/sex/dose, 8-9 weeks old) were administered single oral doses of 1000, 2000, 3000, 4000 mcmol/kg (220, 440, 880 and 1300 mg/kg, 10 ml/kg). The lowest dose was only given to females. A control group receiving tap water was included. Surviving animals were necropsied 3-5 days after dosing. Observations included clinical signs, body weight, gross pathology. Blood samples were taken in satellite animals at a dose level of 120 mg/kg in males and 80 mg/kg in females for determination of prilocaine and o-toluidine plasma levels.

Results:

Mortality: The maximum non-lethal dose was 1300 mg/kg in males and 880 mg/kg in females; the minimum lethal dose was 1300 mg/kg in females and no deaths were observed in males. One animal was killed in moribund condition and two died within 3 hours of dosing.

Gender	Dose (mg/kg)				
	0	220	440	880	1300
Male	0/5	-	0/5	0/2	0/5
Female	0/5	0/5	0/2	0/2	3/5

Clinical signs: Observed clinical signs considered to be drug-related are summarized below. The findings are primarily CNS related, occurred between 15 minutes and 5 hours after dosing, and are typical findings associated with high doses of local anesthetics. Tonic convulsions occurred in females at doses of 880 mg/kg or greater; clonic convulsions occurred at a dos eof 1300 mg/kg.

Clinical signs	Dose (mg/kg)								
	0		220	440		880		1300	
	M	F	F	M	F	M	F	M	F
Decreased motor activity	0/5	0/5	3/5	2/5	2/2	2/2	2/2	5/5	3/5
Ataxia	0/5	0/5	1/5	4/5	2/2	2/2	2/2	4/5	2/5
Half-shut eyes	0/5	0/5	0/5	1/5	2/2	2/2	1/2	2/5	1/5
Increased respiration depth	0/5	0/5	0/5	0/5	2/2	2/2	1/2	2/5	1/5
Piloerection	0/5	0/5	0/5	0/5	1/2	0/2	1/2	3/5	1/5
Tonic convulsions	0/5	0/5	0/5	0/5	0/2	0/2	1/2	0/5	1/5
Loss of righting reflex	0/5	0/5	0/5	0/5	0/2	0/2	1/2	0/5	1/5
Clonic convulsions	0/5	0/5	0/5	0/5	0/2	0/2	0/2	1/5	3/5
Increased respiration rate	0/5	0/5	0/5	0/5	0/2	0/2	0/2	2/5	2/5
Irregular respiration	0/5	0/5	0/5	0/5	0/2	0/2	0/2	1/5	0/5
Noisy respiration	0/5	0/5	0/5	0/5	0/2	0/2	0/2	1/5	0/5
Dyspnea	0/5	0/5	0/5	0/5	0/2	0/2	0/2	0/5	1/5
Increased salivation	0/5	0/5	0/5	0/5	0/2	0/2	0/2	1/5	2/5

Body weight: No drug-related changes in body weight gain were noted.

Gross pathology: No findings related to drug treatment were observed.

Toxicokinetics: Systemic exposure was observed for both prilocaine and o-toluidine. Exposures at the doses assessed were similar in males and females indicating that females receive a greater exposure at comparable doses. The half-life of o-toluidine could not be determined due to the profile of plasma-time curves.

Target dose (mg/kg)	Gender	Compound	Cmax, mean (mcmol/L) (range)	AUC (0-4h) (mcmol.hr/L)	Tmax (min)	t1/2 (hr)
440 mg/kg	M	Prilocaine o-toluidine	54 (50-56) 23 (22-25)	69 46	15 60	2 NA
220 mg/kg	F	Prilocaine o-toluidine	55 (47-68) 25 (10-43)	61 54	15 30	2 NA

Summary of individual study findings: The maximum non-lethal dose was 1300 mg/kg in males and 880 mg/kg in females; the minimum lethal dose was 1300 mg/kg in females and no deaths were observed in males. Clinical observations are CNS related, occurred between 15 minutes and 5 hours after dosing, and are findings associated with high doses of local anesthetics. Systemic exposure was observed for both prilocaine and o-toluidine. Kinetic data indicates that exposure is ~ 2-fold greater in females at comparable doses. Plasma levels at the lowest doses tested in males and females are ~ 30 times greater than the expected maximum total lidocaine and prilocaine plasma level (1.7 mcmol/L) following the proposed use of Oraqix gel.

Toxicology Summary: The sponsor performed two new acute oral toxicology studies with lidocaine and prilocaine in rats for this application. In the lidocaine study, the maximum non-lethal dose was 400 mg/kg in males and 200 mg/kg in females; the minimum lethal dose was 630 mg/kg in males and 400 mg/kg in females. In the prilocaine study, the maximum non-lethal dose was 1300 mg/kg in males and 880 mg/kg in females; the minimum lethal dose was 1300 mg/kg

in females and no deaths were observed in males. Clinical observations in both studies were CNS related, occurred between 15 minutes and 5 hours after dosing, and are findings associated with high doses of local anesthetics. Systemic exposure was observed for both lidocaine and prilocaine as well as their major metabolites (2,6-xylidine and o-toluidine, respectively). Lidocaine exposure was greater in females compared to males but the relative amount of 2,6-xylidine was greater in males. Exposure to prilocaine was ~ 2-fold greater in females at comparable doses. Plasma levels at the lowest doses tested were ~ 4 and 15 times greater in males and females (lidocaine), respectively, and ~ 30 times greater (prilocaine) than the expected maximum total lidocaine and prilocaine plasma level (1.7 mcmol/L) following the proposed use of Oraqix gel.

Studies conducted previously under NDA 19-941 include acute IV toxicity studies of Xylocaine Hydrochloride, Citanest Hydrochloride, and Xylocaine Hydrochloride/Citanest Hydrochloride (1:1) mixture in male mice and male rats, acute subcutaneous toxicity of lidocaine base, prilocaine, and EMLA in male rats, acute dermal toxicity of EMLA cream in rabbits. Intravenous administration of lidocaine was more toxic than prilocaine (1.5 to 2 times in mice and rats; median lethal doses of lidocaine were 24 and 63 mg/kg in rats and mice, respectively; median lethal doses of prilocaine were 45 and 97 mg/kg in rats and mice, respectively). The combination did not increase the lethal intravenous toxicity. Subcutaneous administration of the agents alone or in combination (10% emulsion) produced median lethal doses of > 865-1020 mg/kg and resulted in pronounced local irritation in male rats. Toxic effects of all three formulations included immobility or pronounced lethargy, labored respiration, dyspnea, cyanosis and convulsions. Dermal administration of 43% EMLA Cream (21.5% lidocaine base and 21.5% prilocaine base) in the rabbit (~ 1200 mg/kg of each) produced only slight erythema (2 of 6) of intact skin at 24 hours after dosing. Overall, these studies demonstrated that the acute toxicity of the drug mixtures is probably additive and that neither agent potentiates the other's toxicity. Subcutaneous administration of the agents either alone or together produced severe local irritation in rats at very high concentrations (10% emulsion), and systemic toxicity and local irritation were not observed following 24-hour dermal exposure to a high concentration of the mixture. A rectal administration study in dogs (one month, 2% or 5% EMLA Cream; 5-12.5 mg/kg) under the same NDA produced no local or systemic toxicity at the doses tested. The maximum plasma levels were achieved within 0.5 to 1 hour. Plasma levels of lidocaine (89-238 ng/ml) and prilocaine (31-88 ng/ml) remained below the human toxic level for these drugs (5 mcg/ml).

The formation of methemoglobinemia has been associated with the use of prilocaine. In animal experiments, the maximum methemoglobinemia formation was reached two to three hours after administration of prilocaine and o-toluidine. Some evidence suggests that methemoglobinemia is caused by an additional metabolite like p-hydroxy-toluidine, which has been shown to induce methemoglobinemia in human erythrocytes in vitro. Although methemoglobinemia occurs rarely with single use of prilocaine, caution should be taken with repeated large doses.

Another outstanding issue for this drug product formulation is the use of the purified poloxamers 188 and 407. Poloxamers 188 (and 407 ( ) are constituents of the Periodontal Gel that had not previously been evaluated for safety in connection with other lidocaine and/or prilocaine

formulations. The poloxamers are a series of closely related nonionic block copolymers of the A-B-A type, with a hydrophobic propylene oxide block in the middle (B) and hydrophilic ethylene oxide blocks at the ends. All the poloxamers, as ether alcohols, are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxide included and in molecular weight. Within the poloxamer family, the total molecular weight ranges from about 1000 to over 15000, with the hydrophobic propylene oxide groups constituting between 20% to 90% of the final molecule. The components are added to Oraqix gel to solubilize the active components and give the formulation thermo-reversible gelling properties. The maximum daily dose of purified Poloxamer 188 is [redacted]). The maximum daily dose of purified Poloxamer 407 is [redacted]. Poloxamer 188 is an excipient in numerous drug products using intravenous, subcutaneous and oral routes of administration. Similarly, poloxamer 407 is approved for use in products utilizing the topical, opthalmic, and oral routes of administration. The total daily intake of both poloxamers in the current NDA appears to be greater than that in previously approved products.

In a Pre-NDA meeting held on April 24, 2001, the sponsors were informed that a more detailed description of the purification process of the poloxamers as well as an executed batch record would be needed before the Agency agrees that adequate support is provided for an NDA. Additionally, the nonclinical information in the meeting package support the submission of an NDA and, given sufficient clinical and nonclinical experience with the proposed formulation including lidocaine, prilocaine, metabolites and poloxamers, a bridging study would not be required, pending review by the CMC group. The sponsors were informed that there is no reason to believe that the purified poloxamers will be more toxic than the originally non-toxic, non-purified poloxamers. It was stated that the premise for not requesting a bridging study is that there is no evidence of risk of the unpurified poloxamer. If adequate documentation of safety is not provided, the Agency will need a bridging study. The sponsor was encouraged to provide assurances for the application that the poloxamers have no toxicity before submitting it to the Agency and that resolution of this issue was encouraged prior to submission of the NDA. No agreement was sought on this issue prior to NDA submission.

The sponsor provided the following rationale to support the safety of the proposed use of the purified poloxamers. The two poloxamers have been used in pharmaceutical formulations for many years, and that there is nonclinical and clinical experience to support their safety. The toxicity of the poloxamers is considered to be low, even after IV injection, their irritative potential is minimal, and their absorption and metabolism after oral or mucosal administration is also expected to be minimal. The poloxamers are purified before manufacture of the Periodontal Gel, by reducing the amounts of aldehydes present. This process reduces the number of unsaturated positions on the poloxamer chain which are liable to undergo further reaction, and will also reduce the amounts of prilocaine-aldehyde adducts which may form in the final product. This purification can thus only serve to reduce the risk of any potential toxicity, and in no way detriments the safety of the product. In addition, the sponsor provided references to the relevant DMFs and to numerous published references concerning the safety information about the poloxamers.

The two issues of concern related to the two purified poloxamers are local irritancy and toxicity and systemic toxicity. In terms of the local effects, a toxicity study was performed and reviewed under IND 52,677 and assessed effects of the lidocaine and prilocaine dental gel with poloxamers

(— poloxamer 407 and — poloxamer 188) in anesthetized dogs. The lidocaine/prilocaine gel did not cause any signs of local irritation after animals received up to two doses of 0.1 ml topically in the left gingival sulcus of the lower jaw and 0.4 ml applied to the buccal gingiva within one hour. Application sites were wiped off after one hour and dosing was performed once every other day for five days. Thus, the two poloxamers are adequately qualified for local tissue effects. The systemic effects of the poloxamers are discussed below.

ADME: Studies indicate that absorption of poloxamers 188 and 407 after oral administration will be negligible. Metabolism is also expected to be minimal. An in vitro test in cell cultures demonstrated a lack of metabolism of poloxamer 188 via use of a radioactive label. Following IV injection in rats, almost all of the poloxamer was recovered in the urine within 24 hours. Following oral ingestion, poloxamer 188 was recovered from the feces, indicating a lack of both absorption and metabolism. In dogs, neither molecular weight nor structure of the poloxamer was altered after administration and that following IV injection, poloxamer 188 (250 mg/kg) was excreted quantitatively and unchanged in the urine over a 28 hour period; traces were found in intestinal contents and bile. Following IV administration to dogs of 100 mg/kg poloxamer 407, 68-75% of total dose was recovered within 30 hours, indicating slow excretion; trace amounts were recovered in the feces and 20% was unaccounted for and presumed to be in the interstitial fluid. At 24 hours after a single ip injection of 300 mg, poloxamer 407 was primarily observed in the liver and kidney of rats.

Acute toxicity: Mean lethal doses in rats for poloxamer 188 are 9.4 to > 15 g/kg (oral) and 4-7.5 g/kg (IV). Similar values were observed in mice (15 g/kg, oral; 1-5.5 g/kg, IV), dogs (> 15 g/kg, oral; > 0.5 g/kg, IV) and rabbits (> 15 g/kg, oral; > 1 g/kg, IV). Mean lethal doses in rats for poloxamer 407 were reported to be ~ 15 g/kg and > 10 g/kg. Clinical signs in rats included sedation, prostration, respiratory rales, and severe respiratory depression following oral administration.

Repeat dose toxicity: Three month oral administration studies were performed in rats and dogs using poloxamers 103, 235, 331, and 338 to cover a broad range of total molecular weights. The molecules with lower total/hydrophobe molecular weight and the higher hydrophobe content produced greater toxicity, although only limited toxicity was noted overall. Primary findings included emesis, reduced food consumption, leading to growth depression and mortality. These findings may be related to poor nutrition as the lower molecular weight poloxamers were shown to be non-palatable to rats at high food admixtures and emesis in dogs. The results are summarized below.

Poloxamer	Species	Route	Dose (mg/kg)	Effects
103	Rat	Oral/diet	40	None
			200	None
			1000	Reduced food intake; severe growth depression
	Dog	Oral/capsule	40	None
			200	Some emesis
			1000	Emesis, reduced food intake and growth; resultant death
235	Rat	Oral/diet	40	None
			200	None
			1000	None
	Dog	Oral/capsule	40	None
			200	Some emesis
			1000	Slight weight loss at beginning of study
331	Rat	Oral/diet	40	None
			200	None
			500	None
	Dog	Oral/capsule	40	None
			200	None
			500	None
338	Rat	Oral/diet	200	None
			1000	None
			5000	Slight transient diarrhea
	Dog	Oral/capsule	200	None
			1000	None
			5000	None

These findings were confirmed in target organ studies in rats using poloxamers 103, 182, 235 and 338. The animals were fed increasing concentrations in the feed for 42 days from 1-5% to 3-30%. Poloxamer 182 was administered for 63 days at a concentration of 1%. Similar clinical signs were observed as above and there were no changes in hematologic and urinary parameters or in gross and microscopic pathology.

Long term studies with poloxamers 181, 182 and 188 are summarized below. The primary findings included reduced food consumption, growth depression and deaths at high doses related to poor nutrition. Dogs also demonstrated emesis as well as liver effects (changes in BUN, enzyme activity and weight at doses of 500 mg/kg or greater).

Poloxamer	Species/ Duration	Route	Dose (mg/kg)	Effects
181	Rat/ 14 days	Oral/gavage	200 400	None Slight reduction in food consumption and growth
182	Rat/ 2 years	Oral/diet	40 200 500	None Slight growth depression Severe growth depression, some deaths, reduced testis size and decreased spermatogenesis
	Dog/ 56 doses over 72 days	Oral/capsule	1000	Emesis, excessive weight loss, slight increase in BUN in 1 dog and increased liver weight
	Dogs/ 2 years	Oral capsule	40 200 500	None Emesis, salivation Emesis, salivation, loose stools, weight loss, increased BUN and AP, increased liver weight, deaths
188	Rat/ 6 months	Oral/diet	2300 3800	None None
	Rat/ 2 years	Oral/diet	2300 3800 5600	None Moderate diarrhea Reduced growth, moderate diarrhea
	Dog/ 6 months	Oral/capsule	50 100	None None

Results of IV studies with poloxamer 188 produced no effects at a dose of 100 mg/kg but resulted in foamy lung macrophages, vacuolation of proximal tubular epithelial cells in kidneys and increased lung and kidney weights at doses of 300 mg/kg or greater. Findings in dogs included vacuolation of proximal tubular epithelial cells in kidneys at doses of 250 mg/kg or greater in a 1 month study, as well as increased heart rate, decreased blood cell parameters and vacuolation of the glomeruli (1000 mg/kg). No effects were noted in rabbits after 14 day administration of 50-500 mg/kg.

Genotoxicity: Poloxamer 407 was negative in an Ames assay, Chinese hamster ovary/HGPRT assay, primary rat hepatocyte/DNA repair test and the cell transformation assay using Balb C/3T3 cells. Information on other poloxamers is not available.

Carcinogenicity: The carcinogenic potential of the poloxamers was not specifically investigated although no related findings were reported in a 2 year study with poloxamer 188. Both poloxamers 188 and 407 have been shown to be potent suppressors of carcinogenesis in the colon of rats and mice[1].

[1] Parnaud G, Tache S, Peiffer G, Corpet DE. Pluronic 68 block polymer, a very potent suppressor of carcinogenesis in the colon of rats and mice. British Journal of Cancer 2001: 84 Issue 1: 90-93.

Reproduction: A multigenerational dietary study was performed in rats with poloxamer 331 (100, 250 and 500 mg/kg) and 338 (300, 1000 and 2500 mg/kg) to evaluate effects on fertility and offspring. No effects were noted on the progeny or parental animals.

Local tolerance: Rubbing of 5% and 10% solutions and a paste of poloxamer 188 onto the gums of rabbits and dogs did not produce hyperemia, irritation or microscopic changes. Similar negative results were found following administration of the proposed formulation using unpurified poloxamers in dogs in a study reviewed under IND 52,677.

Safety Assessment of proposed use of unpurified poloxamers 188 and 407:
The maximum expected daily dose of poloxamer 188 is ~ 500 mg (10 mg/kg; 370 mg/m^2), assuming a maximum daily use of 8.5 mg Oraqix Periodontal Gel. Repeat dose studies (6 months) in rats and dogs using oral administration resulted in NOAEL doses of 3800 mg/kg (22800 mg/m^2) in rats and 100 mg/kg (2000 mg/m^2) in dogs. These NOAEL doses provide safety margins of 380 and 10 based upon body weight comparisons and safety margins of approximately 60 and 5 based on body surface area comparisons. Of note, Poloxamer 188, under the name RheothRx, has been tested in Phase 3 clinical trials. High intravenous doses (> 300 mg/kg) have been associated with raised serum creatinine levels, indicative of renal dysfunction. The expected maximum oral intake of poloxamer 188 via the periodontal gel is significantly less than intravenous doses associated with renal toxicity especially considering the relatively low oral absorption of the poloxamers. Thus, the proposed use of poloxamer 188 is acceptable based upon the findings of long-term toxicity studies.

The maximum expected daily dose of poloxamer 407 is ~1320 mg (26 mg/kg; 977 mg/m^2), assuming a maximum daily use of 8.5 mg Oraqix Periodontal Gel. Although repeat dose toxicity studies have not been performed with this specific poloxamer, three month toxicity studies with various poloxamers indicate that poloxamer-related toxicity is greatest with lower molecular weight poloxamers and decreases as molecular weight increases. For example, a table above indicates that toxicities such as emesis and reduced growth were observed with poloxamer 103 (molecular weight 1500) at oral doses of 1000 mg/kg in rats and 200 mg/kg in dogs. Meanwhile, in studies with poloxamer 338 (molecular weight 14000) no toxicity was observed in rats at an oral dose of 1000 mg/kg (6000 mg/m^2) and only transient diarrhea was observed at a dose of 5000 mg/kg. Similarly, no toxicities were observed in dogs at a dose of 5000 mg/kg (100,000 mg/m^2). Of the poloxamers studied for toxicity, poloxamer 407 (molecular weight of 12000) is most similar to poloxamer 338 in terms of molecular weight. If the three month studies with poloxamer 338 were used to assess the potential effects of poloxamer 407, safety margins of 38 (rats) and 192 (dogs) based upon body weight comparisons and safety margins of approximately 6 (rats) and 102 (dogs) based on body surface area comparisons are provided. A worst case scenario could be provided by using the results of three month studies with poloxamer 103 in which NOAEL doses of 200 mg/kg (1200 mg/m^2 in rats, 4000 mg/m^2 in dogs) in rats and dogs could be estimated. If these three month studies were used to assess the potential effects of poloxamer 407, safety margins of approximately 8 in rats and dogs based upon body weight comparisons and safety margins of approximately 1 (rats) and 4 (dogs) based on body surface area comparisons are provided. These safety margins assume that all of the poloxamer 407 is absorbed. Considering that poloxamer 407 is more likely to behave similarly to poloxamer 338 than poloxamer 103 in terms of toxicity, not all of the applied poloxamer 407 will be

systemically available, the animal studies used for safety assessment are of significantly longer duration than the proposed product use, and that there are margins of safety under most comparisons, the proposed use of poloxamer 407 is considered to be acceptable.

Toxicology Conclusions: Newly conducted acute toxicity studies in rats confirmed that lidocaine and prilocaine effects are primarily CNS-related and extremely high doses can induce lethality. In previously conducted studies, administration of a lidocaine/prilocaine dental gel resulted in no local toxicity, while immobility or pronounced lethargy, labored respiration, dyspnea, cyanosis and convulsions were observed with intravenous or subcutaneous administration. No local toxicity was observed following rectal or dermal application. Non-clinical information provided to support the proposed use of poloxamers 188 and 407 is considered to be adequate.

V. GENETIC TOXICOLOGY:

The sponsor provided two genotoxicity studies for prilocaine that were conducted by Astra in 1987. No evidence that these studies were previously reviewed by the Agency was found.

Study title: Mutagenicity evaluation of prilocaine in the Ames Salmonella/mammalian microsome mutagenicity test.

Key findings:

- Prilocaine was negative in the Ames assay under the conditions tested.

Study no: 87072
Study type: Mutagenicity: to detect induction of DNA base pair substitution and frameshift mutations (Ames *et al.*, Mutation Res. 31:347-364, 1975)
Volume # 7, and page #: 153
Conducting laboratory and location: Astra Alab AB
Date of study initiation: October 1987
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug prilocaine, **lot #** 325-1, **radiolabel** none, **and % purity:** —

Formulation/vehicle: Test article in DMSO

Methods:

Strains/species/cell line: *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, TA 102, TA 102 and TA 100. The selected strains did not include *E. coli* WP2 as recommended in OECD guidelines.

Dose selection criteria:

Basis of dose selection: Doses exceeding the OECD recommended limit were used (up to 7150 mcg/plate)

Range finding studies: None performed

Test agent stability: No precipitation observed

Metabolic activation system: rat liver homogenate S9 (10%)

Controls:

Vehicle: DMSO

Negative controls: DMSO

Positive controls: See table below

Salmonella typhimurium strain	Reference Product Used as Positive Control Without Metabolic Activation		Reference Product Used as Positive Control With Metabolic Activation	
	Chemical	Dose (mcg/plate)	Chemical	Dose (mcg/plate)
TA 1535	Sodium Azide	0.5	2-Aminoanthracine	5
TA 1537	9-aminoacridine	75	2-Aminoanthracine	5
TA 1538	2-Nitrofluorene	0.5	2-Aminoanthracine	5
TA 98	2-Nitrofluorene	0.5	2-Aminoanthracine	5
TA 100	Sodium Azide	0.5	2-Aminoanthracine	5
TA102	phenyglyoxal	500	2-Aminoanthracine	5
TA104	phenyglyoxal	500	2-Aminoanthracine	5

Comments: The selected controls were appropriate; positive controls tested in parallel with and without S9

Exposure conditions:

Incubation and sampling times: Incubation period 48 hours

Doses used in definitive study: 2.38, 7.15, 23.8, 71.5, 238, 715, 2380 and 7150 mcg/plate in the first test; 2.44, 7.31, 24.4, 73.1, 244, 731, 2440, 7310 mcg/plate in second test

Study design: The test was performed in two parts. The first part constituted a combined mutagenicity and toxicity study, which was followed by a study designed to confirm the mutagenicity data from the first study. Bacterial samples were incubated overnight in nutrient broth. Aliquots were mixed with agar and maintained with 100 µl of test compound and 500 µl of sodium phosphate buffer or S9 mix. The mixture was poured onto minimal glucose agar plates and incubated 2-3 days.

Analysis:

No. of replicates: 2

Counting method: Manual counting or using ——— counter. Plates were examined macro- and microscopically using a stereo zoom microscope equipped with dark field illumination.

Criteria for positive results: Not stated in the study report

Summary of individual study findings:

Study validity:

1. Frequency of spontaneous back mutations with solvent not significantly different from frequency of back mutations in absolute control for each test
2. Positive response by the positive controls
3. The use of strains *E. coli* WP2 was not included
4. Dose selection was adequate

Study outcome:

The test compound was weakly toxic to strain TA1538 both in the presence and absence of the metabolic activation system at the highest doses (7150 and 7310 mcg per plate).

The number of revertant colonies on the solvent control plates was in the normal range, while the positive control compounds elicited marked increases in the number of revertant colonies. No significant increases in the number of revertant were seen in the presence of test compound under any of the test conditions. In agreement with the sponsor's conclusion, prilocaine was negative in the Ames test under the conditions of this study.

Study title: Mouse micronucleus test of prilocaine

Key findings:

- Prilocaine was negative in the micronucleus test under the conditions tested.

Study no: 87055
Study type: clastogenicity
Volume # 7, and page #: 218
Conducting laboratory and location: Astra Safety Assessment, Sodertalje, Sweden
Date of study initiation: August 1987
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug prilocaine, **lot #** 325-1, **radiolabel** none, **and % purity:** —

Formulation/vehicle: prilocaine in sterile water

Methods:

Strains/species/cell line: NMRI mouse
Dose selection criteria:
Basis of dose selection: Not performed
Range finding studies: Not performed
Test agent stability: No precipitate reported
Metabolic activation system: NA

Controls:

Vehicle: sterile water

Negative controls: physiological saline

Positive controls: methyl methanesulfonate (MMS) dissolved in sterile water (455 mcmol/kg)

Comments: Controls appropriate

Exposure conditions:

Incubation and sampling times: See under Study design below

Doses used in definitive study: 779 and 1558 mcmol/kg (200 and 400 mg/kg); intended to be close to the MTD (20 ml/kg)

Study design: Five males and females per dose group, except positive control, were killed by cervical dislocation 24, 48 and 72 hours after SC administration of test compound. A negative control group was run concurrently. Positive control animals were killed 24 hours after administration. Femoral bone marrow was aspirated and dispersed in a mixture of fetal calf serum and phosphate buffer and smears were made. Slides were coded and examined by light microscopy. The ratio of PCE to all erythrocytes was determined from the first 1000 erythrocytes examined. The frequency of micronucleated cells among both types of erythrocytes was registered concurrently. Altogether, 1000 PCE with and without micronuclei were scored from each animal. The mean incidence of micronucleated PCEs and the ratio of polychromatic to all erythrocytes in treated and positive control groups were compared with the corresponding data from negative control groups. Kruskal-Wallis mean rank test was performed.

Analysis:

No. of replicates: 1

Counting method: light microscopy

Criteria for positive results: not stated

Summary of individual study findings:

Study validity:

1. High dose (400 mg/kg) is not acceptable on its face as a maximum dose for this assay since no indications of toxicity were reported.
2. Controls were appropriate
3. Acceptable PCE:NCE ratio observed
4. Significant increase in frequency of micronucleated PCE in positive control group

Study outcome:

There was no significant increase in the frequency of micronucleated PCE by prilocaine at any dose or timepoint compared to control. The positive control significantly increased the frequency of micronucleated PCE/1000 cells compared to the control frequency. Thus, prilocaine tested negatively in the *in vivo* micronucleus test under the conditions tested in concurrence with the sponsor's conclusions. However, this study is not considered to be valid since the dosing (up to 400 mg/kg) did not appear to reach the MTD or the accepted limit dose of 2000 mg/kg.

Genetic toxicology summary: Genetic toxicology studies for lidocaine were performed and reviewed under NDA 19-941. Studies for prilocaine were submitted to the current NDA and are reviewed currently. Lidocaine was negative in an Ames mutagenicity assay, an in vitro assay for chromosome aberrations in human lymphocytes, and an in vivo mouse micronucleus assay. A metabolite of prilocaine, ortho-toluidine, tested positively in E. coli DNA repair and phage-induction assays (IARC monograph, Volume 27, page 167, 1982). Urine concentrates from rats treated orally with ortho-toluidine were mutagenic in an Ames assay with metabolic activation. Several other tests were negative including an Ames assay (unless tested in the presence of both norharman and metabolic activation), and an in vitro chromosome aberration assay with V79 Chinese hamster cells with metabolic activation. A lidocaine metabolite, 2,6-xylidine, was considered weakly mutagenic (mixed results in different laboratories), and was mutagenic at the thymidine kinase locus. The compound also induced chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cell sat toxic concentrations. It was negative in an unscheduled DNA synthesis assay with rat hepatocytes, a chromosome aberration assay in polychromated eryhtrocytes, and a differential survival assay of DNA repair proficient versus deficient E. coli bacteria in mouse liver, lung, kidney, testis and blood extracts.

An in vitro assessment of the clastogenic potential of prilocaine was not performed and the in vivo micronucleus assay with prilocaine, although negative, is not valid due to inadequate dosing. These studies should be performed as a post-marketing commitment.

Genetic toxicology conclusions: Lidocaine and prilocaine were negative in a series of genotoxicity assays under the conditions of the assays. Metabolites of lidocaine and prilocaine, 2,6-xylidine and o-toluidine, respectively, have tested positively in some genotoxicity assays. An in vitro assessment of the clastogenic potential of prilocaine was not performed and the in vivo micronucleus assay with prilocaine, although negative under the conditions tested, is not valid due to inadequate dose selection. These studies should be performed as a post-marketing commitment.

Labeling recommendations: The product label should include the results of the genotoxicity tests performed with lidocaine, prilocaine and o-toluidine. CDER's Executive CAC determined that positive tumor findings in rats following administration of 2,6-xylidine did not pose a potential carcinogenic risk to humans. Thus, references to positive genotoxicity results for 2,6-xylidine were removed from labeling. See the labeling review at the end of this review for detailed recommendations.

VI. CARCINOGENICITY

Carcinogenicity summary: Carcinogenicity studies with lidocaine, prilocaine or their combination have not been conducted and are not deemed necessary due to the limited duration of exposure expected. The major metabolites (2,6-xylidine from lidocaine and o-toluidine from prilocaine) were carcinogenic in mice and/or rats (see the reviews for NDA 19-941 dated June 19, 1992 and September 28, 1992 by Dr. Dou Lucy Jean for details). 2,6-xylidine produced carcinomas and adenomas in the nasal cavity and a rhabdomyosarcoma (rare) in rats at an oral dose of 150 mg/kg. An increased incidence of subcutaneous fibromas and/or fibrosarcomas was

also noted in males while neoplastic noules of the liver were observed in females. In May 1996, the relevancy of the rat tumor findings to humans was discussed by CDER's Executive Carcinogenicity Assessment Committee (see minutes dated May 14, 1996 under NDA 19-941). The committee concluded that the tumor findings are not relevant to humans and should not be included in the labeling nor should the labeling of other anesthetic products containing lidocaine be revised.

Ortho-Toluidine produced hepatocellular carcinomas or adenomas in female mice and hemangiosarcomas and hemangiomas in both males and females following oral administration oral administration of 150 mg/kg or greater. Additionally, sarcomas of multiple organs, fibromas of subcutaneous tissue and mesotheliomomas, sarcomas of the spleen, transitional cell papillomas and carcinomas of the urinary bladder, and mammary gland fibroadenomas and adenomas were observed in rats at oral doses of 150 mg/kg or greater. IARC has classified o-toluidine as a chemical in group 2B, meaning that there is sufficient evidence of carcinogenicity in experimental animals but inadequate data for humans. A cancer risk assessment by Gary Williams, M.D. (1984) concluded that the extended and high levels of exposure needed and the types of tumors seen suggest that o-toluidine is a weak carcinogen in animals. Additionally, an assessment by the US EPA[2] indicated the hazard ranking of o-toluidine to be low.

Sponsor's rationale supporting the safety of the expected exposure to o-toluidine:
The sponsor refers to an accepted value for permissible daily, lifelong exposure to o-toluidine of 2 ppm (9 mg/m^3) in the air (Threshold Limit Value, ACGIH). This limit is given as an 8-hour Time-Weighted Average (TWA) for o-toluidine and applies for daily human exposure to o-toluidine throughout an entire working life. This level may be exceeded for short periods. This value corresponds to a daily exposure of 45 mg or 0.9 mg/kg when the inhaled air volume over an 8 hour period is assumed to be 10 m^3 and the actual lung uptake is assumed to be 50%. Based upon this calculated single day exposure, an allowable annual exposure is 10,800 mg or 216 mg/kg per year assuming 240 working days per year.

In calculating the maximum expected dose of o-toluidine via conversion of prilocaine to o-toluidine, the maximum recommended dose of Oraqix is 8.5 g gel. The bioavailability of prilocaine in man varies from 20-40% and the maximum value of 40% absorption was used in sponsor's calculations. Thus, the absorbed dose of prilocaine from an administration of 8.5 mg Oraqix gel is 85 mg. If 100% of a prilocaine dose is metabolized to o-toluidine, the conversion will be 1:1 on a molar basis. This gives a conversion on a weight basis of about 50% for prilocaine base or 40% for prilocaine HCl. Urinary recovery in a clinical trial in healthy volunteers showed that 37% of a given SC dose of prilocaine was excreted as o-toluidine and its hydroxy metabolites, supporting a 1:1 conversion on a molar basis or a 40-50% conversion on a weight basis. Using these assumptions, the sponsor calculated that the amount of o-toluidine formed in man from the prilocaine absorbed after the application of 8.5 g of the Periodontal Gel is 32 mg/m^2 (~ 43 mg) after a single treatment. The human exposure was calculated by the sponsor as 8.5 g gel x 25 mg/g prilocaine base x 40% absorption which results in 85 mg of absorbed prilocaine. A 50% conversion to o-toluidine results in a systemic administration of ~ 43 mg o-toluidine or 0.86 mg/kg (32 mg/m^2). The yearly maximum exposure assuming a maximum

[2] Evaluation of the Potential Carcinogenicity of o-Toluidine. (1988). United States Environmental Protection Agency.

of 4 treatment sessions/year was used to calculate the "yearly exposure" in humans of 130 mg/m^2 (~174 mg).

A comparison of the expected maximum daily exposure to o-toluidine from Oraqix Periodontal Gel (43 mg) with the permitted daily exposure under the ACGIH TLV (45 mg) results in a ratio of 1.05. Additionally, comparing the expected maximum annual exposure to o-toluidine from Oraqix Periodontal Gel (428 mg) with the permitted daily exposure under the ACGIH TLV (10,800 mg; 7990 mg/m^2) results in a ratio of 62.

The sponsor also indicates that the mouse and rat carcinogenicity studies resulted in exposure to o-toluidine that were 14 (mouse) and 28-fold (rat) higher than exposures in humans for a single dose of 8.5 g gel at the lowest dose tested (150 mg/kg). The exposure ratios increase to 1300 and 2500-fold higher for a yearly exposure. These exposure ratios are on the basis of body surface area and assume 40% absorption of prilocaine and 100% conversion to o-toluidine.

Assesment of sponsor's rationale: In a letter dated August 25, 2000, the sponsor was asked to provide the final o-toluidine content in the final drug product for clinical use. Also, the amount present should be limited to the lowest feasible concentration or no greater than the permitted exposure level (PEL) or Threshold Limit Value (TLV) for Chemical Substances and Physical Agents Biological Exposure Indices.

The sponsor originally proposed a drug product specification for o-toluidine of NMT——— which is similar to that of the approved EMLA Cream. This specification could result in a maximum daily intake of o-toluidine from the drug product of 3.4 mg/day based on a maximum daily application of 8.5 g of Oraqix Periodontal Gel. Dr. Michael Theodorakis, the CMC reviewer, orally informed this reviewer that the sponsor subsequently agreed to lower the drug product specification to ——— and that this lower specification would be recommended. The lower drug product specification of ——— would result in a maximum daily intake of o-toluidine from the drug product of 2.1 mg/day.

The sponsor's calculations which estimate a daily intake of o-toluidine of 43 mg from the maximum daily use of Oraqix are not considered to be acceptable. Dr. David Lee, the Biopharmaceutics reviewer for this NDA, indicated that the information submitted by the sponsor to support their claim of a maximum of 40% drug absorption of the drug components for the human use of Oraqix gel were not adequate. Thus, the maximum exposure to o-toluidine was re-calculated with a conservative assumption of 100% absorption and resulted in a maximum expected daily intake of 107 mg o-toluidine from the use of Oraqix in one administration period. Thus, the maximum daily intake of o-toluidine through conversion from prilocaine and the 1.7 mg allowed under a drug product specification of ——— results in a maximum daily intake of ~ 109 mg. Although the maximum expected daily intake of 109 mg o-toluidine is greater than that allowed under the ACGIH TLV value of 45 mg/day, the expected annual exposure to o-toluidine through use of Oraqix of 435 mg (109 mg/dose, expected maximum use of 4 times per year) is ~ 25-fold lower than the levels allowed annually under the ACGIH TLV (10,800 mg).

The only other permissible exposure limit identified is a Florida State Drinking Water Guideline of 50 mcg/l or 0.1 mg/day assuming a daily intake of 2 liters of water per day. The expected daily

intake of o-toluidine via the Oraqix Periodontal Gel is ~ 1100 times greater than the permitted daily intake in water and 12-fold greater than that allowed on an annual basis. Although the ACGIH value is a permitted level for an occupational setting that typically assumes greater risk than a patient population and the expected single daily intake of o-toluidine through Oraqix Periodontal Gel exceeds the Florida State Guideline, the overall carcinogenic risk from o-toluidine to humans via the use of Oraqix Periodontal Gel is expected to be minimal since the proposed clinical use is acute in nature. It should be noted that under current ICH Guidelines, carcinogenicity studies would not typically be requested for this product.

Carcinogenicity conclusions: Carcinogenicity testing for lidocaine and prilocaine have not been performed and are not deemed necessary due to the limited duration of exposure for this drug product. However, the major metabolites (2,6-xylidine from lidocaine and o-toluidine from prilocaine) were carcinogenic in long-term studies performed in mice and/or rats. CDER's Executive CAC concluded that the tumor findings are not relevant to humans and should not be included in the product labeling. In regards to o-toluidine, the sponsor was asked to provide the final o-toluidine content in the final drug product for clinical use. Also, the amount present should be limited to the lowest feasible concentration or no greater than the permitted exposure level (PEL) or Threshold Limit Value (TLV) for Chemical Substances and Physical Agents Biological Exposure Indices. The maximum annual exposure to o-toluidine is ~ 25-fold below the allowable annual intake using a TLV determined by ACGIH. The overall carcinogenic risk from o-toluidine to humans via the use of Oraqix Periodontal Gel with the drug product specification of ——— is expected to be minimal since the proposed clinical use is acute in nature.

Labeling recommendations: The product label should state that a carcinogenic assessment of lidocaine or prilocaine has not been performed. In addition, the tumorigenic findings related to o-toluidine should be discussed in the product label.

VII. REPRODUCTIVE TOXICOLOGY:

Reproductive toxicology summary: The potential of the lidocaine/prilocaine combination to affect reproductive parameters was evaluated in an embryo-fetal developmental study performed under NDA 19-941 (see review dated June 19, 1992). Subcutaneous administration of an aqueous mixture containing lidocaine HCl and prilocaine HCl at 1:1 ratio up to 40 mg/kg each produced no teratogenic, embryotoxic or fetotoxic effects. The potential effects of subcutaneously administered lidocaine (30 mg/kg) in rats was also evaluated and found to produce no evidence of harm to the fetus. Studies with intramuscularly administered prilocaine (300 mg/kg) in rats also revealed no harm to the fetus. Additionally, subcutaneously administered prilocaine and lidocaine (up to 30 mg/kg) produced no evidence of impaired fertility during an eight month administration period in which animals were allowed to mate three times with the first mating occurring after 2 months treatment. Approved labeling for EMLA Cream classifies the product as Pregnancy Category B.

It does not appear that a fertility study with lidocaine, embryo-fetal developmental studies in rabbits with lidocaine or prilocaine, or pre- and post-embryo-fetal developmental studies with

lidocaine or prilocaine have been conducted. Thus, the sponsor should conduct these studies. Conduct of these studies as a Phase 4 commitment is acceptable as these products are currently marketed in various formulations and since the sponsor was not previously notified of these requirements.

Reproductive toxicology conclusions: A lidocaine/prilocaine formulation produced no embryo-fetal developmental effects at subcutaneous doses up to 40 mg/kg each. Similarly, lidocaine (up to 30 mg/kg SC) and prilocaine (up to 300 mg/kg, IM) alone produced no fetal effects; prilocaine also had no effect on fertility. The sponsor should conduct fertility studies with lidocaine, embryo-fetal developmental studies in rabbits with lidocaine or prilocaine, and pre- and post-embryo-fetal developmental studies with lidocaine and prilocaine as Phase 4 commitments.

Labeling recommendations: The product labeling should include the current information concerning the reproductive effects of lidocaine and prilocaine, alone and in combination. The pregnancy category should be classified as "B".

VIII. SPECIAL TOXICOLOGY STUDIES:

Summary of special toxicology studies:
A local toxicity study, performed and reviewed under IND 52,677, assessed effects of lidocaine and prilocaine dental gel (2.5% each; doses of 25-50 mg/dog; 1-2 hours exposure) in anesthetized dogs. The lidocaine/prilocaine gel did not cause any signs of local irritation after animals received 0.1 ml topically in the left gingival sulcus of the lower jaw and 0.4 ml applied to the buccal gingiva parallel to the first application. Application sites were wiped off after one hour and dosing was performed once every other day for five days.

Other studies performed under NDA 19-941 assessed the local irritation potential of lidocaine and prilocaine emulsions and creams on the skin and eye of rabbits and the vagina of dogs. A 10-day (single instillation) eye irritation study of 5% and 10% emulsions produced a dose-dependent severe and prolonged irritation. Examination revealed marked hyperemia of the conjunctiva, swelling with eyelids half-closed, profuse fluid and exudate discharge, pitted corneal surface and necrosis of the nictitating membrane. A 24-hour intact skin irritation study of 5% and 10% emulsion with occlusive dressing produced mild, transient irritation at 5% and erythema at 10% that persisted up to 24 hours in some animals. A 20-day intact and abraded skin irritation study of 5% EMLA Cream and emulsions produced very slight erythema and slight edema that was comparable to a placebo formulation. A 20-day vaginal irritation study of 5% EMLA Cream (1 ml daily) showed slight erythema with no apparent change to the vaginal micro-flora. No significant local toxicity was observed in female dogs administered a 2% cream (1% lidocaine, 1% prilocaine) when the test article was placed in the lumen following uterine centesis.

In a published study by Anniko and Schmidt[3], instillation of EMLA into the middle ear of guinea pigs caused severe morphological damage to the organ of Corti in the first 4 mm from the round window. Derangement of the stereocilia was found further up the cochlea.

[3] Anniko and Schmidt. Acta Otolaryngo. 105:255-265. 1988.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Overall Summary and Evaluation:
The pharmacology of the local anesthetics lidocaine and prilocaine is well known. The anesthetics block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels. Lidocaine and prilocaine have similar pharmacological profiles although some differences are noted. Although the sponsor performed no pharmacology studies with the current formulation, studies performed with the drug combination at similar concentrations in a cream or emulsion under NDA 19-941 produced concentration-related analgesia upon a 60-minute contact with both unabraded and abraded skin.

The primary effects of lidocaine and prilocaine related to safety pharmacology include CNS and cardiovascular effects at plasma levels exceeding ~ 10 μmol/L (5 mg/L) for either compound. Plasma levels following administration of Oraqix Periodontal Gel are expected to be well below the plasma levels at which these adverse findings are observed.

Lidocaine and prilocaine bases are absorbed rapidly through mucous membranes, intact and damaged skin, and from the intestines and respiratory tract. The hydrochlorides are absorbed rapidly after parenteral administration, but absorption through intact skin or mucous membranes is poor. Both lidocaine and prilocaine are absorbed and extensively distributed and metabolized. The major metabolites include MEGX and 2,6-xylidine (lidocaine) and o-toluidine (prilocaine). Elimination half-lives across species for both compounds are in the range of 1-2 hours.

Newly conducted acute toxicity studies in rats confirmed that lidocaine and prilocaine effects are primarily CNS-related and extremely high doses can induce lethality. In previously conducted studies, administration of a lidocaine/prilocaine dental gel resulted in no local toxicity, while immobility or pronounced lethargy, labored respiration, dyspnea, cyanosis and convulsions were observed with intravenous or subcutaneous administration. No local toxicity was observed following rectal or dermal application. Non-clinical information, provided to support the proposed use of poloxamers 188 and 407, is considered to be adequate.

Lidocaine and prilocaine were negative in a series of genotoxicity assays under the conditions of the assays. Metabolites of lidocaine and prilocaine, 2,6-xylidine and o-toluidine, respectively, have tested positively in some genotoxicity assays. An in vitro assessment of the clastogenic potential of prilocaine was not performed and the in vivo micronucleus assay with prilocaine, although negative under the conditions tested, is not valid due to inadequate dose selection. These studies should be performed as a post-marketing commitment.

Carcinogenicity testing for lidocaine and prilocaine have not been performed and are not deemed necessary due to the limited duration of exposure for this drug product. However, the major metabolites (2,6-xylidine from lidocaine and o-toluidine from prilocaine) were carcinogenic in long-term studies performed in mice and/or rats. CDER's Executive CAC concluded that the tumor findings are not relevant to humans and should not be included in the product labeling. In

regards to o-toluidine, the sponsor was asked to provide the final o-toluidine content in the final drug product for clinical use. Also, the amount present should be limited to the lowest feasible concentration or no greater than the permitted exposure level (PEL) or Threshold Limit Value (TLV) for Chemical Substances and Physical Agents Biological Exposure Indices. The maximum annual exposure to o-toluidine is ~ 25-fold below the allowable annual intake using a TLV determined by ACGIH. The overall carcinogenic risk from o-toluidine to humans via the use of Oraqix Periodontal Gel with the drug product specification of ——— is expected to be minimal since the proposed clinical use is acute in nature.

A lidocaine/prilocaine formulation produced no embryo-fetal developmental effects at subcutaneous doses up to 40 mg/kg each. Similarly, lidocaine (up to 30 mg/kg SC) and prilocaine (up to 300 mg/kg, IM) alone produced no fetal effects; prilocaine also had no effect on fertility. The sponsor should conduct fertility studies with lidocaine, embryo-fetal developmental studies in rabbits with lidocaine or prilocaine, and pre- and post-embryo-fetal developmental studies with lidocaine and prilocaine as Phase 4 commitments.

A local toxicity study of lidocaine and prilocaine dental gel (2.5% each; doses of 25-50 mg/dog; 1-2 hours exposure) in anesthetized dogs did not cause any signs of local irritation after animals received 0.1 ml topically in the left gingival sulcus of the lower jaw and 0.4 ml applied to the buccal gingiva parallel to the first application. Application sites were wiped off after one hour and dosing was performed once every other day for five days. A 10-day (single instillation) eye irritation study of 5% and 10% emulsions produced a dose-dependent severe and prolonged irritation. Examination revealed marked hyperemia of the conjunctiva, swelling with eyelids half-closed, profuse fluid and exudate discharge, pitted corneal surface and necrosis of the nictitating membrane. A 24-hour intact skin irritation study of 5% and 10% emulsion with occlusive dressing produced mild, transient irritation at 5% and erythema at 10% that persisted up to 24 hours in some animals. A 20-day intact and abraded skin irritation study of 5% EMLA Cream and emulsions produced very slight erythema and slight edema that was comparable to a placebo formulation. A 20-day vaginal irritation study of 5% EMLA Cream (1 ml daily) showed slight erythema with no apparent change to the vaginal micro-flora. No significant local toxicity was observed in female dogs administered a 2% cream (1% lidocaine, 1% prilocaine) when the test article was placed in the lumen following uterine centesis. Instillation of EMLA into the middle ear of guinea pigs caused severe morphological damage to the organ of Corti. Derangement of the stereocilia was found further up the cochlea.

Conclusions:

Lidocaine and prilocaine are local anesthetic compounds that block conduction by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na^+ that normally is produced by a slight depolarization of the membrane due to direct interaction with voltage-gated Na^+ channels.

The primary effects of lidocaine and prilocaine include CNS and cardiovascular effects at plasma levels exceeding ~ 10 µmol/L (5 mg/L) for either compound.

Lidocaine and prilocaine bases are absorbed rapidly through mucous membranes and are extensively distributed and metabolized. The major metabolites include MEGX and 2,6-xylidine (lidocaine) and o-toluidine (prilocaine). Elimination half-lives across species for both compounds

are in the range of 1-2 hours.
Two new acute oral toxicology studies with lidocaine and prilocaine in rats revealed no unexpected drug-related toxicities; clinical observations in both studies were CNS related. The sponsor has provided adequate safety qualification for the proposed use of the purified poloxamers 188 and 407.
Both lidocaine and prilocaine tested negatively in various genetic toxicology studies, although a complete battery has not been performed for prilocaine.
Carcinogenicity studies have not been performed with either lidocaine or prilocaine. Ortho-Toluidine, the primary metabolite of prilocaine, produced positive findings in both rats and mice. However, the overall carcinogenic risk from o-toluidine to humans via the use of Oraqix Periodontal Gel is expected to be minimal since the proposed clinical use is acute in nature and the expected annual exposure is significantly less than that allowed under accepted exposure limits.
No evidence of reproductive effects was observed with these compounds although a complete battery of studies has not been performed.
No evidence of local irritation was noted when a lidocaine/prilocaine mixture was administered to the gingival sulcus of dogs. Administration of the EMLA mixture produced severe irritation while the irritation was more mild when applied to skin.

General Toxicology Issues:
No unexpected toxicities were observed in acute toxicity studies in rats with lidocaine and prilocaine at maximum tolerated doses. The sponsor has provided adequate information to support the proposed use of the purified poloxamers 188 and 407.

An in vitro assessment of the clastogenic potential of prilocaine was not performed and the in vivo micronucleus assay with prilocaine, although negative under the conditions tested, is not valid due to inadequate dose selection. These studies should be performed as a post-marketing commitment.

The sponsor should conduct fertility studies with lidocaine, embryo-fetal developmental studies in rabbits with lidocaine or prilocaine, and pre- and post-embryo-fetal developmental studies with lidocaine and prilocaine as Phase 4 commitments.

Recommendations:

1. This NDA is considered to be approvable from a nonclinical perspective.

2. The following deficiencies in the nonclinical program should be addressed by the sponsor as Phase 4 commitments:
   a) An in vitro assessment of the clastogenic potential of prilocaine and an in vivo micronucleus assay of prilocaine should be performed.
   b) A fertility study with lidocaine, embryo-fetal development studies in rabbits with lidocaine and prilocaine, and pre- and post-embryo-fetal development studies with lidocaine and prilocaine should be performed.

Labeling:

The sponsor's proposed wording for the Carcinogenicity, Mutagenicity and Impairment of Fertility, and Pregnancy sections of the Label are reproduced below:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis - Cancer studies have not been performed on either lidocaine or prilocaine, due to the area and duration of therapeutic use of these drugs. Chronic oral toxicity studies of *o*-toluidine, a metabolite of prilocaine, in mice (150 to 2400 mg/kg or 450 to 7200 mg/m^2) and rats (150 to 800 mg/kg or 900 to 4800 mg/m^2) have shown that this compound is a carcinogen in both species.

The lowest given doses of *o*-toluidine in these animal studies (150 mg/kg, or 450 mg/m^2 in mice and 900 mg/m^2 in rats) have first been compared with the estimated exposure to *o*-toluidine in man after application of about 3.5 g Oraqix Periodontal Gel. A further comparison has also been made with the estimated exposure to *o*-toluidine in man after the Maximum Recommended Dose (MRD) of Oraqix at any one treatment session, i.e. 5 cartridges or 8.5 g gel. For these calculations, all doses have been expressed as mg/m^2 and 50 kg has been used as the body weight of a small adult. The factors for converting a mg/kg dose to mg/m^2 are 3, 6 and 37 for mice, rats and adult humans, respectively. The systemic bioavailability of prilocaine after application of 8.5 g Oraqix to the oral/gingival mucosa was shown to be 20 to 40% (95% confidence interval). Thus, a prilocaine absorption of 40% has been used in the calculations of exposure to *o*-toluidine. Complete conversion of prilocaine to its metabolite *o*-toluidine on a molar basis is assumed. This gives a conversion on a weight basis of about 50% for prilocaine base (dependent on the molecular weights, i.e. 220 for prilocaine base and 107 for *o*-toluidine).

Exposure to *o*-toluidine was calculated to be about 35 and 69-fold higher in mice and rats, respectively, at the lowest given doses in the oral carcinogenicity studies, than in humans treated with 3.5 g of Oraqix, based on a single dose. Based on a yearly exposure (once daily dosing for a year in animals and a realistic maximum of 4 treatment sessions/year in humans), the safety margins increased to 3200 and 6300-fold when comparing the exposure animals:man. Similarly, exposure in animals was calculated to be about 14 and 28-fold higher (in mice/rats) than that in humans after a single administration of the MRD of Oraqix, or 1300 and 2500-fold higher in animals for a yearly exposure.

Mutagenesis - The mutagenic potentials of both lidocaine and prilocaine have been tested in the Ames Salmonella/mammalian microsome test *in vitro* and in the mouse micronucleus test *in vivo*. In addition, lidocaine has been tested for structural chromosome aberrations in human lymphocytes *in vitro*. There was no indication of any mutagenic effects in these studies.

o-Toluidine, a metabolite of prilocaine, showed positive results in *Escherichia coli* DNA repair and phage-induction assays at a concentration of 0.5 µg/mL. Urine concentrates from rats treated with *o*-toluidine (300 mg/kg, or 1800 mg/m^2 orally) were mutagenic to *Salmonella typhimurium* in the presence of metabolic activation. Several other tests on *o*-toluidine, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation, and single strand breaks in DNA of V79 chinese hamster cells, were negative.

Impairment of Fertility: See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats with subcutaneous or intramuscular administration of an aqueous solution of lidocaine HCl, prilocaine HCl or a 1:1 (weight/weight) mixture of these two compounds. Complete absorption of lidocaine and prilocaine can be assumed for these routes of administration, and thus the given doses in animals in mg/kg are compared with the systemically bioavailable doses of lidocaine and prilocaine (approximately 40% for both compounds) in mg/kg after treatment with the MRD of Oraqix (8.5 g) to the oral/gingival mucosa, in a 50 kg adult. There was no evidence of harm to the fetus after subcutaneous treatment of rats with 30 mg/kg lidocaine; about 18 times higher than the systemically bioavailable dose of lidocaine after application of the MRD of Oraqix. Reproduction studies with prilocaine did not reveal any evidence of impaired fertility or harm to the fetus after intramuscular treatment of rats with 300 mg/kg intramuscularly; about 180 times higher than the systemically bioavailable dose of prilocaine after application of the MRD of Oraqix. Similarly, embryo-fetal toxicity studies in rats have been performed with subcutaneous administration of a mixture of lidocaine and prilocaine. At 40 mg/kg of each compound (80 mg/kg of the combination), a dose about 24 times higher than the systemically bioavailable dose of the two local anesthetics together after application of the MRD of Oraqix, no teratogenic, embryotoxic, or fetotoxic effects were observed.

There are, however, no adequate and well-controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, Oraqix should be used during pregnancy only if clearly needed.

The sponsor's proposed labeling should be revised as follows:

Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or prilocaine. Chronic oral toxicity studies of *o*-toluidine, a metabolite of prilocaine, have shown that this compound is a carcinogen in both mice and rats. The tumors included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. These findings were observed at the lowest tested dose of 150 mg/kg/day or greater over 2 years (estimated daily exposures in mice and rats were approximately 6 and —times, respectively, the estimated exposure to o-toluidine at the maximum recommended human dose of 8.5 g of Oraqix gel on a mg/m^2 basis). Thus, the no effect dose is less than 6-— times the estimated exposure to o-toluidine at the maximum recommended human dose. Complete conversion of prilocaine to its metabolite o-toluidine on a molar basis is assumed. This gives a conversion on a weight basis of about 50% for prilocaine base (dependent on the molecular weights, i.e. 220 for prilocaine base and 107 for o-toluidine).

Mutagenesis: The mutagenic potentials of both lidocaine and prilocaine have been tested in the Ames Salmonella/[illegible] test *in vitro* and in the mouse micronucleus test *in vivo*. In addition, lidocaine has been tested for structural chromosome aberrations in human lymphocytes *in vitro*. There was no indication of any mutagenic effects in these studies.

o-Toluidine, a metabolite of prilocaine, was positive in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated orally with 300 mg/kg *o*-toluidine were mutagenic to *Salmonella typhimurium* in the presence of metabolic activation. Several other tests on *o*-toluidine, including reverse mutations in five different *Salmonella typhimurium* strains with or without metabolic activation, and single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Impairment of Fertility: See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats with lidocaine, prilocaine and a 1:1 (weight:weight) mixture of the two compounds. There was no evidence of harm to the fetus with subcutaneous doses of lidocaine up to 30 mg/kg (estimated exposure was approximately equal to the maximum recommended human dose of Oraqix gel on a mg/m^2 basis). Following intramuscular doses of prilocaine up to 300 mg/kg (estimated exposure was approximately [illegible] times the maximum recommended human dose of Oraqix gel by on a mg/m^2 basis), there was no evidence of impaired fertility or harm to the fetus. Similarly, subcutaneous administration of a lidocaine and prilocaine mixture of 40 mg/kg of each compound (estimated exposures were approximately [illegible] times the expected lidocaine and prilocaine exposures at the maximum recommended human dose of Oraqix gel on a mg/m^2 basis) produced no teratogenic, embryotoxic, or fetotoxic effects. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Oraqix should be used during pregnancy only if [illegible].

X. APPENDIX/ATTACHMENTS:

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Timothy McGovern
11/18/02 02:03:04 PM
PHARMACOLOGIST